THE EPIDEMIOLOGY OF HAND OSTEOARTHRITIS

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ABSTRACT

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Background
Radiographic osteoarthritis most commonly affects joints in the hands, with osteoarthritis at the finger interphalangeal joints (IPJs) thought to be a different subset to that at the first carpometacarpal joint (CMCJ). The thesis aimed to identify risk factors for hand (particularly IPJ) osteoarthritis.

Methods
Systematic reviews and Delphi studies were performed to identify risk and prognostic factors for incident and progressive IPJ osteoarthritis.

A risk prediction model for incident radiographic IPJ osteoarthritis (Kellgren Lawrence (KL) ≥2 in ≥1 IPJ), and a prognostic model for the progression of IPJ osteoarthritis (increase of KL ≥1 in ≥1 IPJ), in the Chingford 1000 Women Study were developed. As the prognostic model performance was poor, the model was revised in the Johnston County Osteoarthritis (JoCo) Project.

The burden of hand injury requiring hospital admission, and the association between hand injury and osteoarthritis was investigated in cricketers.

Results
From the systematic review and Delphi study for incident IPJ osteoarthritis, older age in women, female sex, family history, and injury were important risk factors. Whilst for the progression of IPJ osteoarthritis, older age and family history were important prognostic factors.

The prediction model included 459 participants (257 with osteoarthritis at 10 years). Older age, manual occupation, and first CMCJ osteoarthritis were important predictors.

The prognostic model included 195 participants (181 progressing at 10 years), with no prognostic factors found to be important. Following revision, female sex was found to be an important factor.

Over ten years, 9,188 cricketers presented with hand injuries, most commonly in young adults, with thumb and little finger injuries, particularly fractures and dislocations. Hand injury was associated with osteoarthritis.

Conclusion
IPJ osteoarthritis might be a continuum of first CMCJ osteoarthritis. Manual occupation and injury could be targeted to decrease disease risk, whilst older age is an unmodifiable risk factor.

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This thesis is dedicated to my parents, who,
in a world where education is not always considered a right for women,
have tried to ensure it is.

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IMPACT OF COVID-19 ON THIS DPHIL

When the COVID-19 pandemic began to affect the UK, in March 2020, I was in the second year of my DPhil. My DPhil was impacted by the pandemic, though the scope of my work did not change. Firstly, the department (Botnar Research Centre) was closed for in-person working, and for the last 15 months of my DPhil I was working from home. This means that the amount of collaborative research I could pursue was hugely decreased, and, communication with collaborators was slowed down as it relied on e-mail and virtual meetings. I was also due to attend the DPhil module on Observational Research, which was cancelled. This means the amount of direct teaching I received was decreased. Further, a number of conferences I was due to present at were cancelled or postponed (IOC 2020, OARSI 2020), limiting my ability to disseminate my research results, and minimising my networking opportunities.

As a practising medical doctor, I was also designated as a *key worker*, and received a request to return to clinical work during the pandemic. I chose to work clinically part-time in the NHS, working between two to seven days per month from March 2020 up to the time of my *viva voce* (July 2021). To aid in understanding this pandemic from an academic perspective, I also joined multiple collaborative research projects, particularly with CovidSurg and Observational Health Data Sciences and Informatics (OHDSI) (publications listed following).

PUBLICATIONS ARISING FROM THIS THESIS

Shah K, Cai H, Lane JCE, Collins GS, Arden NK, Furniss D, Filbay SR. Prognostic factors for finger interphalangeal joint osteoarthritis: A systematic review. Rheumatology (Oxford). 2021;60(3):1080-1090.

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Shah K, Arden NK, Silman AJ, Furniss D, Collins GS. Development and Validation of a Prediction Model for Incident Radiographic Finger Interphalangeal Joint Osteoarthritis. Osteoarthritis Research Society International (OARSI) Virtual World Congress. 2021; Denver, Colorado (virtual).

Shah K, Arden NK, Silman AJ, Collins GS, Furniss D. Development of Risk Calculators for Hand Osteoarthritis and Invasive Treatment. Surgical Research Society Virtual Meeting. 2021; Dublin, Ireland (virtual).

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Shah K, Furniss D, Collins GS, Peirce N, Arden NK, Filbay SR. The odds of Hand Pain and Osteoarthritis in individuals with cricket-related hand injury. Osteoarthritis Research Society International (OARSI) World Congress. 2019; Toronto, Canada.

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Shah K, Bullock GS, Silman AJ, Furniss D, Arden NK, Collins GS. Calculating Risk of Hand Osteoarthritis Progression at Ten years through a Prediction Model. Annual European Congress of Rheumatology European Alliance of Associations for Rheumatology (EULAR). 2021; Paris, France (virtual).

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OTHER PUBLICATIONS DURING THIS DPHIL

Duarte-Salles T, Vizcaya D, Pistillo AM, Casajust P, Sena AG, Lau LYH, Prats-Uribe A, Ahmed WU, Alshammari TM, Alghoul H, Alser O, Burn E, You SC, Areia C, Blacketer C, DuVall S, Falconer T, Fernandez-Bertolin S, Fortin S, Golozar A, Gong M, Tah EH, Huser V, Iveli P, Morales DR, Nyberg F, Posada JD, Recalde M, Roel E, Schilling LM, Shah NH, Shah K, Suchard MA, Zahng L, Zhang Y, Williams AE, Reich CG, Hripcsak G, Rijnbeek P, Ryan P, Kostka K, Preito-Alhambra D. 30-Day Outcomes of Children and Adolescents With COVID-19: An International Experience. Paediatrics. 2021; *In press.*

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ABBREVIATIONS

95% CI: 95% confidence interval
ACR: American College of Rheumatology
AIC: Akaike information criterion
APACHE: Acute Physiology, Age, Chronic Health Evaluation
AUC: Area under the receiver operating characteristic curve
BMI: Body mass index
BSSH: British Society for Surgery of the Hand
Chingford Study: The Chingford 1000 Women Study
CHWS: Cricket Health and Wellbeing Study
CMCJ: Carpometacarpal joint
C-statistic: Concordance-statistic
DIPJ: Distal interphalangeal joint
ED: Emergency department
EWCB: England and Wales Cricket Board
GP: General Practitioner
HRT: Hormone replacement therapy
ICC: Intraclass coefficient
ICD: International Classification of Disease
IPJ: Interphalangeal joint
IQR: Interquartile range
JoCo Project: The Johnston County Osteoarthritis Project
KL: Kellgren-Lawrence
LASSO: Least absolute shrinkage and selection operator
MAR: Missing at random
MCAR: Missing completely at random
MNAR: Missing not at random
MICE: Multiple imputation by chained equations
MSK: Musculoskeletal
NHANES: National Health and Nutrition Examination Survey
NHS: National Health Service
OARSI: Osteoarthritis Research Society International
OR: Odds ratio
PIPJ: Proximal interphalangeal joint
PMLE: Penalised maximum likelihood estimation
PRISMA: Preferred Reporting Items for Systematic review and Meta-analysis
QUIPS: Quality in Prognostic Studies
RCS: Restricted cubic spline
REC: Research Ethics Committee
REDCap: Research Electronic Data Capture
SD: Standard deviation
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
TRIPOD: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis
UK: United Kingdom
USA: United States of America
VAED: Victorian Admitted Episodes Dataset
VEMD: Victorian Emergency Minimum Dataset
VISU: Victoria Injury Surveillance Unit

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1 CHAPTER 1: INTRODUCTION

1.1 The pathology of osteoarthritis

Osteoarthritis is a degenerative joint disease, with a complex disease process. Joints are mechanical structures, and there is a large evidence base to suggest biomechanical forces contribute to the development and progression of osteoarthritis. In particular, abnormal joint loading and stress can lead to microtrauma, whilst acute trauma can cause cartilage or meniscal damage. These all can cause cartilage breakdown and contribute to unusually high forces across joints. Initially, there is enough compensation from regeneration, but ultimately, there are both catabolic and anabolic processes ongoing simultaneously, and there is a failure to remodel and repair on a molecular level and degenerative changes dominate (1).

Historically, osteoarthritis was thought to only affect the articular cartilage, though it is now widely accepted that it encompasses the whole joint (2, 3). Inflammation of the synovium, synovitis, is recognised as an early important component of the disease process (3). Synovitis is associated with the development of osteoarthritis, and, in patients with knee osteoarthritis, also shown to be associated with its progression (4, 5). Synovitis can occur after joint trauma, and might also be associated with other pro-inflammatory systemic conditions. Synovitis also occurs during the sub-clinical stage of the disease (6). This has been visualised through magnetic resonance imaging and immunohistochemical studies (7-11). Clinical biomarkers for synovitis include c-reactive protein, and immune-mediated cells such as B cells and T lymphocytes are also raised (12-15).

Osteoarthritis with high amounts of joint inflammation occurs particularly in the hand interphalangeal joints (IPJs). IPJ osteoarthritis can present with bony swellings due to osteophytosis, which are seen as bony spurs on plain film radiographs (16, 17). These bony swellings are termed nodes, and are known as Heberden's nodes in the distal interphalangeal joints (DIPJs), and as Bouchard's nodes in the proximal interphalangeal joints (PIPJs). Nodal osteoarthritis can be associated with severe joint inflammation (often referred to as 'an inflammatory phenotype', in which pain, stiffness, and soft tissue swelling occur but without radiographic changes) and with accelerated joint erosion (often referred to as 'an erosive phenotype', with both subchondral erosions on radiographs and with pain, stiffness, and soft tissue swelling) (18-20). It is also possible for patients with nodal osteoarthritis to have an overlap between both inflammatory and erosive phenotypes, such in patients whom have an erosive phenotype but only show inflammatory signs at different stages of the disease (21).

Inflammation further stimulates the release of degradation enzymes from chondrocytes, which themselves lead to the further breakdown and loss of articular (hyaline) cartilage (1). This exposes the underlying subchondral bone, which itself may have already begun its remodelling during the early stages of the disease. Sclerotic changes and bone cysts develop, leading to an increase in the subchondral bone thickness, architectural changes in the trabecular bone of the subchondral region, and the formation of osteophytes (22). However, osteoarthritis is not always progressive, and can become stable. Stability might be intermittent or last for prolonged time periods, with changes between these phases being identified through dynamic imaging, such as bone scintigraphy (23).

1.2 Anatomical sites affected by osteoarthritis

Osteoarthritis can affect joints in the spine, shoulders, wrists, hands, hips, knees, ankles, and feet. There is ongoing debate about whether osteoarthritis is a generalised disease, affecting multiple joint sites, or whether it is a joint specific disease (24). In particular, evidence from genetic studies suggests osteoarthritis affecting the knees and hands, for example, is a polyarticular disease (25). However, the differences in the incidence and prevalence of osteoarthritis across different joint sites, and the differences in the demographic of people affected by osteoarthritis at different joint sites, would suggest it might affect individual joints.

Incidence of osteoarthritis at different anatomical sites

The incidence of a disease is the number of new cases per unit population over a defined time period. Measuring the incidence of osteoarthritis, at any joint, can be challenging. This is be because osteoarthritis is sometimes considered a polyarticular disease, and the onset of osteoarthritis at one joint may influence the development of osteoarthritis at other joint. It is also because it is difficult to determine the exact onset of the pathology, and instead, the incidence of osteoarthritis is often defined as the first onset of clinical symptoms. This is frequently measured using routinely collected data from healthcare databases, captured when people present to clinicians for management and treatment options of their symptoms. The most characteristic symptoms of osteoarthritis are pain, stiffness, joint instability (particularly in weight bearing joints, such as the knee), and reduction in function or movement (26). Nevertheless, osteoarthritis can also be measured using both/ either radiographic or symptomatic, or clinical (for example, the presence of Heberden's nodes) classification criteria for academic studies. A more detailed description of diagnostic criteria and classification used for osteoarthritis, particularly for the hands, is detailed below (sections 1.3.1 and 1.5).

In the United Kingdom (UK), the incidence rate of consultations with a general practitioner (GP) for osteoarthritis at any site has been reported as 7.2 per 1,000 persons annually (27), using Read Codes. Read Codes have been used in GP practices in the National Health Service (NHS) between 1985 and 2018 (28), and are likely to include both radiographic and symptomatic osteoarthritis. Similarly, in the Netherlands, the incidence rate of consultations are between 5.4 to 9.7 and in British Columbia is 11.7 per 1,000 persons annually (29, 30).

To better understand the incidence of osteoarthritis at individual joints, particularly the knee, hip, and hand, a systematic review of studies between 1993 and 2005 has previously been performed (though a meta-analysis was not possible due to heterogenous classification criteria) (31). The systematic review reported the cumulative incidence of radiographic knee osteoarthritis was between 12.6% to 15.6%, whilst of radiographic hip osteoarthritis was between 9.3% and 33.0%, and for hand osteoarthritis it was 83% (31). However, study follow up periods were much longer for hand osteoarthritis, and study participants were younger (31). In a more recent study assessing the incidence of clinically diagnosed osteoarthritis through primary care databases in Spain, the incidence rates were largely different to results reported in the systematic review above (26). The Spanish study reported the incidence rate of clinically diagnosed knee osteoarthritis to be the highest at 6.5 per 1,000 person-years, followed by hand osteoarthritis at 2.4 per 1,000 person-years, and then hip osteoarthritis at 2.1 per 1,000 person-years (26). However, the incidence rates of osteoarthritis at each joint were shown to vary with age and sex, and this is discussed in more detail below. Nevertheless, the incidence of hand osteoarthritis is comparatively high, though it appears to be least commonly studied in the literature.

Prevalence of osteoarthritis at different anatomical sites

The prevalence is the number of cases with disease (either new or existing) at either a specific time point (i.e.- point prevalence), or over a specific time period (i.e.- period prevalence). The prevalence of osteoarthritis can be measured through the presence of symptoms or signs during clinical examinations, through self-reported questionnaires to detect symptoms or, more commonly, using imaging modalities, in particular, plain film radiographs. The period prevalence is most often measured using plain film radiographs, as joint changes seen on radiographs are likely to either stay the same or worsen, whilst symptoms might fluctuate, and at times not be present. A more detailed description of criteria used to classify osteoarthritis on plain film radiographs, particularly for the hands, is detailed below (section 1.5).

The prevalence of osteoarthritis varies between different anatomical sites, exemplified through a systematic review and meta-analysis of 63 studies published between 1995 and 2010 (31). This review summarised data on the prevalence of osteoarthritis in the hip, knee and hand, using all diagnostic criteria (self-reported definitions, radiographic definitions, and symptomatic definitions) (31). The systematic review identified 43 studies assessing the prevalence of knee osteoarthritis, with six studies defining it using self-reported definitions, 25 studies using radiographic definitions, and 14 using symptomatic definitions (some studies used multiple definitions). In the meta-analysis, the prevalence of knee osteoarthritis was found to be 23.9%. There were 27 studies assessing the prevalence of hip osteoarthritis (four using self-reported definitions, 19 using radiographic definitions, and four using symptomatic definitions), with the meta-analysis reporting a prevalence of 10.9%. Similarly, there were 20 studies assessing hand osteoarthritis prevalence (two using self-reported definitions, 14 using radiographic definitions, and five using symptomatic definitions), with the meta-analysis finding a prevalence of 43.3%. The results suggest that hand osteoarthritis has the highest prevalence.

Demographics of people affected by osteoarthritis at different joint sites

Characterising the demographics of people with osteoarthritis at individual joint sites might provide some insight into whether osteoarthritis affects individual joints, or whether it is a polyarticular disease. The incidence of osteoarthritis in the knees, hips, and hands has been described by the study of primary healthcare data in Spain (26). This study reported that females had a higher incidence rate of clinically diagnosed osteoarthritis across individual knee, hip and hand joints, compared to males. The largest differences between sexes was seen in the hands, with an incidence rate of 3.5 per 1,000 person-years in females and 1.3 per 1,000 person-years in males, followed by the knees (females: 8.3, males: 4.6 per 1,000 person-years), and then the hips (females: 2.4, males: 1.7 per 1,000 person-years) (26). Similarly, this study reported differences in incidence rates by age and sex per individual joint. The results described in females, in the hands, the incidence rates rapidly increased at ages 40 to 45 years, peaking at 60 years, whilst in the knees and hips the incidence rates increased at ages 50 to 70 years for both, peaking at 75 to 80 years in the knees, and 80 to 85 years in the hips (26). In males, across all joints, the incidence rates increased with age and peaked after the age of 85 years (26). These results suggest hand osteoarthritis occurs in much younger participants than in the knee or hip, particularly in females around the time of menopause.

Similarly, the age and sex demographics of patients with prevalent osteoarthritis who have sought treatment has been described using primary healthcare data, by *Versus Arthritis* (previously known as Arthritis Research UK), the largest charity dedicated to supporting patients with arthritis in the UK (32). Their results reported that for osteoarthritis across each of the knee, hip, and hand, the highest prevalence of patients seeking treatment were in the 45 to 64 years' age category (Table 1.1). In the hands, this decreased as age increased, whilst in the knee and hip, this decreased later, between ages 65 to 74 years, and then increased in patients aged 75 years or older (Table 1.1). Across all joints, for each age category, more females than males sought treatment, and this was particularly pronounced for hand osteoarthritis in the 45 to 64 years category (Table 1.1).

Table 1.1: Demographics of patients seeking treatment for osteoarthritis at different joints

Age category (years)	**Sex**	**Number of people (million)**		
		Hand osteoarthritis	Knee osteoarthritis	Hip osteoarthritis
45 to 64	Female	0.62	1.25	0.55
	Male	0.27	1.11	0.29
65 to 74	Female	0.24	0.65	0.31
	Male	0.13	0.51	0.21
≥75	Female	0.20	0.75	0.48
	Male	0.10	0.45	0.22

Data is shown for the number of people who have sought treatment for osteoarthritis from general practice (primary healthcare) over seven years in the UK. All data is adapted from *Versus Arthritis* (32).

These studies suggest that there are age and sex differences between patients who require healthcare management for knee, hip, and hand osteoarthritis. In particular, patients with hand osteoarthritis are more likely to be younger and more likely to be female, compared to patients with either knee or hip osteoarthritis. Both the differences in incidence and prevalence of hand osteoarthritis compared to either knee or hip osteoarthritis, and the differences in demographics of patients who develop hand osteoarthritis compared to knee or hip osteoarthritis suggest that the aetiology of hand osteoarthritis might be different, and that extrapolating data from osteoarthritis at other anatomical sites would not be appropriate. Despite the prevalence of hand osteoarthritis being high, most studies have excluded hand osteoarthritis data. Therefore, this thesis will focus on hand osteoarthritis.

1.3 Hand osteoarthritis

Hand osteoarthritis can affect any joint in the hands, including the DIPJs, PIPJs, base of thumb (first carpometacarpal joint (CMCJ)), or the metacarpophalangeal joints.

1.3.1 Diagnosing hand osteoarthritis

In clinical practice, clinicians need to make a judgement regarding whether or not a patient presenting with particular symptoms or clinical signs might have osteoarthritis as there is no absolute diagnostic test for hand osteoarthritis.

Diagnosis based on symptoms

Symptoms patients often complain about are pain, stiffness, and loss of function (26). Pain in hand osteoarthritis, similar to other joints, is often described as a dull aching pain, which is relieved by exercise. Pain from hand osteoarthritis is also known to vary, and can show a diurnal pattern, similar to rheumatoid arthritis (33). Hand osteoarthritis can also lead to stiffness, which is often worse in the morning, before exercise. This pain and stiffness can contribute towards loss of hand or finger function, with patients complaining of reduced grip strength and decreased range of motion. This functional loss limits activities of daily living, and may contribute to the reported poor mental health and quality of life scores in patients with hand osteoarthritis (34). However, there is currently no gold-standard diagnostic criteria for pain, stiffness, or loss of function, for hand osteoarthritis.

Diagnosis based on clinical examination

On clinical examination, patients might be found to have tenderness on palpation, soft tissue swelling, and bony enlargement and nodes. Tenderness and soft tissue swelling are signs of active joint inflammation, related to the pain that patients often present with. Patients might also present with nodes, such as Heberden's nodes on the DIPJs, or Bouchard's nodes on PIPJs. Nodes can grow, as the underlying osteophytes enlarge over time, up to a maximum size (16, 17). As osteophytes and nodes progress, they may be associated with stiffness and reduced joint function. Commonly, they are also associated with patients' dissatisfaction of the aesthetic appearance of their hands. This dissatisfaction is itself associated with an increase in negative illness perceptions and with higher rates of depression and anxiety, and poorer health-related quality of life scores, adding to the morbidity associated with hand osteoarthritis (35, 36).

Diagnosis based on imaging

Plain film radiographs are the most commonly used imaging modality to diagnose hand osteoarthritis. Typically, radiographs are assessed for the presence of osteophytes, subchondral cyst formation, bony sclerosis, and they can also show joint deformity. Ultrasound is not routinely used to diagnose osteoarthritis, but can be used to assess joint inflammation, such as joint effusion and synovitis. Ultrasound can also be used to guide joint injections, during the management of osteoarthritis.

1.3.2 Management of osteoarthritis

Osteoarthritis can also be managed at isolated joint types, and, as are there are no systemic disease modifying treatments options, the disease is managed symptomatically. Management options can be classified into conservative (non-surgical) or invasive (surgical). Conservative options most commonly include the use of analgesics, both systemically (such as the use of oral analgesia, for example, paracetamol), and locally (such as the application of topical analgesia, for example, ibuprofen gel). Conservative management options also include alternative treatments, which are targeted to isolated joints or joint types.

For hand osteoarthritis, there are multiple alternative treatment options, and treatment options for IPJ osteoarthritis in particular have been identified in a recent systematic review (37). These include the use of hand therapy techniques, such as hand exercises (38-42), the use of electromagnetic therapy (43), joint protection protocols (41), and the use of an orthosis for immobilisation (44, 45); thermal treatment options, such as paraffin bath therapy (46), spa therapy (47), and balneotherapy (48); low-level laser therapy (49-51); and other alternative techniques, such as relaxation and yoga (52), wearing a pressure gradient glove (53), and playing the keyboard (54). These can be used alongside analgesia, which can be taken orally or applied topically (55).

Invasive options also target individual joints, and are used in patients with structural changes in whom conservative treatments to do not adequately manage pain (56). For hand osteoarthritis, these most commonly include intra-articular steroid (glucocorticoid) injections, arthrodesis, and arthroplasty at individual joints. In 2018, the European League Against Rheumatism guidelines for the management of hand osteoarthritis were updated with revisions in the recommendations for these invasive options (56). In particular, these guidelines advise the use of glucocorticoid injections in patients with painful IPJ osteoarthritis (56). The guidelines also recommend the use of arthrodesis (joint fusion) for osteoarthritis in DIP osteoarthritis, and the use of arthroplasty (for example, using silicone or pyrocarbon implants) for PIPJ osteoarthritis (56). Though similar invasive treatment options exist for first CMCJ osteoarthritis, the nature of invasive management means that it is almost always performed on individual joint sites, targeting isolated symptomatic disease.

1.4 The public health burden from osteoarthritis

Osteoarthritis leads to pain and loss of function, rendering it a leading cause of disability worldwide (57-59). Most of the data assessing the public health burden from osteoarthritis excludes hand osteoarthritis, and comes from knee and hip osteoarthritis. The disability burden has effects both on the individual level and on the greater societal level, and can be classified into direct, indirect, and intangible costs (60). Direct costs include those for health-care provision and treatment, whilst indirect costs are those affecting the working ability of individuals with osteoarthritis, such as the socioeconomic cost of absenteeism and earlier retirement. Intangible costs, such as those from pain and a decrease in quality of life, affect individuals and are often less well described.

Estimating the overall cost of osteoarthritis can be difficult, due to different systems of health-care provision and methods of costing worldwide. However, data from across the United States of America (USA), Canada, UK, France, and Australia, have all shown the total cost of osteoarthritis to account for 1 to 2.5% of the gross national product (61). In the USA, direct healthcare costs have been estimated at approximately $6,200 more in a person with osteoarthritis compared to a person without osteoarthritis, leading to an estimated total cost of $185.5 billion annually for all osteoarthritis patients (62). In Australia, the majority of these costs are due to inpatient hospital stays and rehabilitation or residential care (63). Furthermore, the direct costs of treating osteoarthritis have been reported to be equivalent to the direct cost of treating coronary artery disease, both accounting for 2% of all health-care costs, in France (64).

When considering indirect costs, people with osteoarthritis are almost twice more likely to be absent from work compared to those without osteoarthritis, such that people with osteoarthritis are absent for an average of three days annually (65). This results in approximately $500 absenteeism costs per capita per year, with a total cost of $10.3 billion annually in the USA (65). The cost of absenteeism due to osteoarthritis is twice that due to asthma, and similar to that for migraine (65).

However, absenteeism is not considered to be the main contributor to the indirect costs of osteoarthritis, accounting for only 4% of productivity costs, which itself accounts for two thirds of indirect costs (63). Instead, in Australia, the main contributor to indirect costs has been reported as a decrease in employment rate (63).

Given the high costs associated with osteoarthritis, there has been wide interest in better characterising and managing the disease. Within the UK, in 2011, the Chief Medial Officer's annual report recommended the need for more rigorous monitoring of musculoskeletal disease, which includes osteoarthritis (66). Since then, the Royal College of Surgeons of England launched an independent Commission on the Future of Surgery. This commission aimed to identify medical and technological advances which could change surgical care over the next 20 years (67). In particular, when describing the predicted 'burden' of disease in the future, the commission identified degenerative musculoskeletal diseases, and in particular osteoarthritis, as a field in which the prevalence of disease and the need for surgical management is likely to grow (67).

Interest in hand osteoarthritis in particular has grown in recent years. In 2017, the British Society for Surgery of the Hand (BSSH) and the James Lind Alliance developed a priority setting partnership, through the Oxford Biomedical Research Centre. The aim was to survey both clinicians and patients or carers, to identify common hand and wrist surgery research priorities. The results found that hand and wrist osteoarthritis was one of the conditions which generated the most interest, and, when selecting the top 10 priorities in hand and wrist surgery research, gaining a better understanding of the most effective non-surgical treatments for osteoarthritis in the hand and fingers was chosen (68).

1.5 Classifying hand osteoarthritis for academic studies

For the purposes of research, academic studies must be able to classify whether or not a study participant has hand osteoarthritis. In clinical practice, diagnostic criteria are used, most often on patients who present with symptoms. However, as symptoms and signs can vary between and within patients, and there are no gold-standard diagnostic criteria, classification criteria have instead been developed. Classification criteria are themselves based on individual features or components of the disease, themselves called criteria. Classification criteria can either be based on clinical symptoms or signs, or, more commonly, on findings from plain film radiography.

Clinical classification criteria

The gold-standard clinical classification criteria for hand osteoarthritis are the American College of Rheumatology (ACR) criteria to diagnose hand osteoarthritis (69) (Figure 1.1). These criteria have been validated and has been shown to have a sensitivity of 0.94 and a specificity of 0.87 (69). However, when developing these criteria, the control group was patients with rheumatoid arthritis, and therefore the diagnosis of osteoarthritis focuses on symptoms in the second and third fingers and the base of thumb, essentially diagnosing patients who had hand symptoms but did not have rheumatoid arthritis. These classification criteria also include only the thumb, second (index), and third (middle) fingers, ignoring the ring and little fingers. Moreover, IPJs and first CMCJs are grouped, not distinguishing disease at either of these anatomical sites.

Hand pain, aching or stiffness for most days of the last month, plus 3 of the below 4 criteria:

1. Hard tissue enlargement of ≥2 out of 10 hand joints from bilateral second and third DIPJs and PIPJs, and first CMCJs
2. Metacarpophalangeal joint swelling in ≤2 joints
3. Hard tissue enlargement in ≥2 DIPJs
4. Deformity in ≥1 out of 10 hand joints from bilateral second and third DIPJs and PIPJs, and first CMCJs

Figure 1.1: American College of Rheumatology criteria for hand osteoarthritis

Taken from the American College of Rheumatology criteria (69)

Other clinical classification criteria for hand osteoarthritis describe a loss of function. This is often reported as a part of patient reported outcome measures, which can be used to assess the impact of the disease on the lives of patients, and ascertain how they experience the condition. A commonly used questionnaire to capture patient reported outcome measures from hand osteoarthritis is the Function Index for Hand Osteoarthritis (70, 71). This questionnaire largely focusses on the loss of function patients might experience from hand osteoarthritis. Other questionnaires, such as the Arthritis Impact Measurement 2 Short Form questionnaire, the Score for Assessment and Qualification of Chronic Rheumatoid Affections of the Hands questionnaire and the Australian/Canadian Osteoarthritis Health Index, have also been validated to measure functional loss from hand osteoarthritis (72-75).

Radiographic classification criteria

The role of imaging modalities to diagnose hand osteoarthritis is to discern structural joint changes and reactive and destructive changes, such as inflammation, in the surrounding tissues. The gold standard imaging modality for the morphological assessment of hand osteoarthritis is plain film radiographs (x-rays) (76). Other modalities, such as ultrasound, magnetic resonance imaging (MRI) and scintigraphy can also be used, and might be useful in subsets of osteoarthritis which show inflammatory or erosive features. However, inflammatory and erosive osteoarthritis are beyond the scope of this thesis.

Ten different radiographic classification criteria for hand osteoarthritis were identified in a recent systematic review (77). These classification criteria rely on grading severity of disease with reference to an atlas, a collection of standardised images which allows reproducible gradings between radiograph readers. Atlases are used to diagnose osteoarthritis at individual joints, either by assessing multiple features and presenting a composite (or global) score, or by assessing the presence or absence of individual features. These features reflect the disease process of osteoarthritis, evaluating loss of joint space, subchondral sclerosis, cysts, the presence of osteophytes, and malalignment across the joint.

1) Kellgren Lawrence atlas:

The oldest atlas is the Kellgren Lawrence (KL) atlas, developed between the 1950s and 1970s. The KL atlas has been defined as the ‘gold standard’ by the World Health Organisation for use in epidemiological studies (78). The first description of what would later become the KL atlas was published in 1957, with the atlas being released in 1963 (79, 80). The KL atlas can be used to assess the IPJs, first CMCJ, and the metacarpophalangeal joints. It uses a composite score of four osteoarthritic features, to determine the severity of osteoarthritis at a joint across five grades (Figure 1.2) (79, 80).

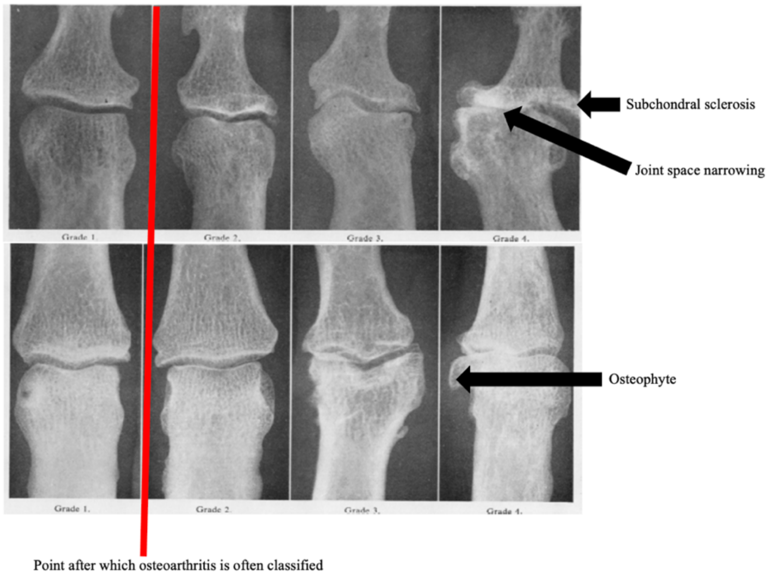

Figure 1.2: Kellgren Lawrence classification of IPJ osteoarthritis

Image adapted from the Kellgren Lawrence atlas (79, 80)
Upper images are for DIPJs, lower images are for PIPJs

Grade 0 (not shown): No joint space or reactive changes
Grade 1 (left of the red line): Doubtful narrowing of joint space and possible osteophytic lipping
Grade 2 (right of the red line): Definite osteophytes and possible narrowing of joint space
Grade 3: Moderate osteophytes, definite narrowing of joint space, some sclerosis and possible deformity of bone ends
Grade 4: Large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends.

A KL grade of two or more is often considered as the threshold for the classification of osteoarthritis, though the KL atlas has not yet been validated for use in the hands (79, 80). In 1977, Lawrence used slightly different descriptions of the grading (81), and these have led to some inconsistencies over time. In particular, in Lawrence's 1977 version of the atlas, grade 1 requires a 'minute' osteophyte, grade 2 requires 'unimpaired' joint space, and grade 4 does not describe sclerosis (81). This could lead to slightly different interpretations of diagnostic criteria being used across studies.

The KL atlas also gives great emphasis to the presence of osteophytes in the early stages of the disease, even though the exact sequence of osteoarthritis change at the joint is not yet fully understood (82). Both KL grades 1 and 2 include the presence of osteophytes in their definitions, despite this interval being the point after which osteoarthritis is diagnosed. Therefore, other diagnostic criteria for osteoarthritis have been developed, assessing individual osteoarthritis features.

2) Altman atlas

The Altman atlas (also known as the Osteoarthritis Research Society International (OARSI) atlas) is another commonly used atlas. The Altman atlas was initially developed in 1995 (83), though, due to gallery proofs not being available, it was replaced with an updated version in 2007 (84). The Altman atlas can only be used to assess osteoarthritis in the IPJs, and the first CMCJs. The atlas individually scores the presence of osteophytes, joint space narrowing, sclerosis, alignment, and erosions/ cysts. These detailed descriptions were intended to better describe the process of osteoarthritis, instead of just marking its absence or presence (84). However, the Altman atlas does not have a standardised threshold after which osteoarthritis is diagnosed.

The following eight atlases are less commonly used in the hand osteoarthritis literature (77):

3) Verbruggen score (Anatomical phases, used to describe erosive IPJ osteoarthritis) (85)

4) Verbruggen score (Anatomical lesions) (85)

5) Eaton atlas (used to stage first CMCJ and the scaphotrapeziotrapezoidal joint for treatment) (86)

6) Gent University Scoring System (for erosive IPJ osteoarthritis) (87)

7) Kessler atlas (88),

all of which use a composite score.

8) Burnett atlas (89)

9) Kallman atlas (90)

10)Lane atlas (91),

all of which score individual features.

The literature shows that studies reporting the incidence and prevalence of hand osteoarthritis most commonly use radiographic classification criteria (31). However, patients presenting to healthcare are most often diagnosed based on symptoms or signs elicited during clinical examinations. There is also known to be conflicting evidence for the incidence and prevalence of hand osteoarthritis between that based on radiographic classification criteria and that based on clinical diagnosis (92-96). To overcome this, academic studies sometimes use classification criteria based on both clinical symptoms or signs and on radiographic classification criteria. For example, a study might assess pain, alongside the radiographic presence of osteoarthritis defined using the KL atlas (79, 80).

Within hand osteoarthritis, there is no widely used method for assessing only joint pain. However, in studies of lower limb osteoarthritis, a commonly used measure of joint pain is the National Health and Nutrition Examination Survey (NHANES) pain question, used alongside radiographic classification criteria (97, 98). The NHANES pain question was developed as part of the NHANES, a national survey carried out in the USA to assess the health and nutritional status of adults. The NHANES pain question assesses the presence of joint pain. However, there is no one standard NHANES pain question, and instead different version of the NHANES pain question exist, with the duration of pain and the period of recall differing across versions of the NHANES pain question (97).

1.6 Joints in the hand affected by osteoarthritis

There are multiple joints in the hand which can be affected by osteoarthritis. The most common joint types affected by osteoarthritis in the hands are the first CMCJs and the finger IPJs. Historically, osteoarthritis at any hand joint was considered part of the same disease process. However, more recently, it is thought that osteoarthritis affecting the IPJs and osteoarthritis affecting the first CMCJs may be different disease subsets, each with different aetiology and risk factors (76). Evidence supporting this theory comes from a) differences in their clinical presentation, with nodes being more common at IPJs (i.e.- nodal osteoarthritis), b) data showing isolated disease at one of these joint types only, and c) cluster analysis studies reporting the preferential spread of osteoarthritis to the same joint type as that already affected. Compared to first CMCJ osteoarthritis, there has been much less focus on IPJ osteoarthritis, and therefore, this thesis will primarily focus on IPJ osteoarthritis.

<u>Nodal IPJ osteoarthritis</u>

Nodal osteoarthritis typically occurs in the IPJs, though, rarely, can occur in the first CMJs. It can also be associated with an inflammatory phenotype or an erosive phenotype, though this is outside the scope of this thesis. Nodal osteoarthritis is thought to have a strong hereditary component. This was first described in a study of 68 families, which reported that in women with Heberden's nodes, their mothers were twice more likely, and their sisters three times more likely, than the general population to also have Heberden's nodes (99). A further study from the same group then found that there was a hereditary component in both men and women, though this was stronger through the maternal compared to the paternal lineage, with a greater frequency of people having Heberden's nodes if their mothers were affected (100). When considering Bouchard's nodes, they too were found to be more common in both men and women who had relatives with nodal osteoarthritis (101). More recently, a study of female twins has calculated that in monozygotic twins there is a higher correlation of Heberden's nodes within the pair, compared to within a dizygotic twin pair (intraclass correlation coefficient (ICC): 0.49 for monozygotic twin pair, and 0.24 for dizygotic twin pain) (102). Nodal osteoarthritis also shows genetic anticipation, whereby symptoms occur at a younger age in offspring compared to the index cases (103).

Heberden's nodes are also thought to be associated with both the incidence and the progression of knee osteoarthritis, suggesting it might be part of a polyarticular osteoarthritis subtype. In a 12 year study assessing the development of radiographic knee osteoarthritis, Heberden's nodes were associated with a six times increased odds of cartilage loss in the knees (104). When considering the progression of knee osteoarthritis, a meta-analysis identifying prognostic factors for the progression of radiographic knee osteoarthritis found that the odds of radiographic knee osteoarthritis was increased two-fold in patients with Heberden's nodes (105). The number of Heberden's nodes, and symmetrical Heberden's nodes, also each increase the association with both the incidence and the progression of radiographic knee osteoarthritis (106).

Isolated disease by joint type

Osteoarthritis can affect both the IPJs and the first CMCJ. However, it is also recognised that isolated osteoarthritis does occur, affecting only one particular joint type in the hand. For example, a study of over 15,000 adults recruited from five GP practices in the UK found that though a group of participants had both IPJ and first CMCJ osteoarthritis, other groups of participants also had osteoarthritis at isolated joint types within the hand (107). Specifically, 7.6% of participants had isolated symptomatic nodal IPJ osteoarthritis, 5.5% had isolated symptomatic non-nodal IPJ osteoarthritis, and 22.5% had isolated symptomatic first CMCJ osteoarthritis (107). When a similar population-based study was performed in Italy, results there reported higher rates of isolated symptomatic IPJ osteoarthritis, with approximately 21% of participants having isolated nodal IPJ osteoarthritis, similar to the prevalence of isolated first CMCJ osteoarthritis (25.4% of participants) (108).

Cluster analysis studies

Once osteoarthritis occurs in one joint type in the hands, it also preferentially spreads within that joint type. This preferential spread was first described in the Chingford 1000 Women Study (Chingford Study), a population-based cohort study of middle aged women in the UK (109). In the Chingford Study, 1003 women between the ages of 45 to 64 years were recruited from a GP practice in North East London, with 967 (96.4%) having hand radiographs taken and read using the KL atlas at the baseline year (80). Using a logistic regression, the prevalence of osteoarthritis at each individual hand joint, for grades KL ≥2 and KL ≥3, were calculated. This was then used to calculate the estimated number of hand joints with osteoarthritis each participant was expected to have, stratified by age. The actual number of hand joints with osteoarthritis per participant was then determined, and the expected versus observed frequencies were assessed. Finally, the association between osteoarthritis at different joint groups (ray: same digit in unilateral hand; row: same joint type in unilateral hand; symmetry: same individual joint bilaterally) was assessed for patterns.

The Chingford Study analysis found that the observed frequencies for the number of hand joints with osteoarthritis per participant, for both KL ≥2 and KL ≥3, were far higher than the expected frequencies (80). This suggested that osteoarthritis clusters in joints, with participants experiencing radiographic osteoarthritis in more hand joints than expected. When investigating the patterns of this clustering, the study reported that osteoarthritis most commonly clustered symmetrically, with a greater than 13 times increases odds of osteoarthritis occurring in the same individual joint in the contralateral hand compared to any other joint (80). The next most common pattern of clustering was by row (joint type), with a five to 10 times increased odds of osteoarthritis occurring in a DIPJ if another DIPJ already had osteoarthritis (80). Following this, the next most common clustering pattern was by ray (within a digit), with a four to six times increased odds of osteoarthritis in either a PIPJ or a DIPJ if one of these within the same finger already had osteoarthritis (80). Comparatively, the association between osteoarthritis in the first CMCJ and the IPJs was much smaller and only significant for osteoarthritis of KL ≥2 (odds ratio (OR): 1.2 to 1.6) (80).

These findings were reproduced in the Framingham Study, in which both male and female participants were assessed for both radiographic (defined as KL ≥2) and radiographic symptomatic hand osteoarthritis (defined as KL ≥2 with the presence of pain, aching, or stiffness, on most days of the last month), in individual joints (110). The analysis performed replicated that in the earlier Chingford Study analysis, though was also stratified by sex and used the absence of radiographic symptomatic osteoarthritis in the same individual joint in the contralateral hand in men as the reference group. The results included 976 study participants, and reported the observed frequency of osteoarthritis, in both men and women, was higher than expected (110). Similarly, both radiographic and radiographic symptomatic osteoarthritis most strongly clustered by symmetry, followed by, and then by ray (110).

Similarly, a third study was performed to assess the pattern of joint involvement for hand osteoarthritis assessed clinically (defined as the presence of Heberden's nodes, Bouchard's nodes, or squaring at the first CMCJ), in a national cohort of approximately 3,000 British adults (111). The study also reported a higher observed versus expected number of joints with osteoarthritis, and clustering patterns most strongly by symmetry, followed by row, and then by ray (111).

These three studies all provide insight into the way osteoarthritis in the hands spreads, and indicates that there are possible subsets within hand osteoarthritis which could be based on joint types. This spread is thought not to be random, following a genome-wide linkage analysis performed in the Framingham Study, investigating linkage regions for radiographic osteoarthritis (defined as KL ≥2, and also using specific Framingham criteria for the presence of osteophytes and the presence of joint space narrowing (112)) (113). The results reported two linkage regions for radiographic DIPJ osteoarthritis, and two different linkage regions for radiographic first CMCJ osteoarthritis (113). These results support the theory that hand osteoarthritis may be a disease made of multiple joint-based subtypes. Therefore, it would be appropriate to perform joint specific studies when investigating hand osteoarthritis.

1.7 Risk factors for osteoarthritis

Understanding risk factors for osteoarthritis, and specifically IPJ osteoarthritis, is important for multiple reasons. Firstly, the public health and associated cost burden of osteoarthritis is recognised to be significantly high. In order to develop preventative measures to decrease the incidence and prevalence of the disease, the causes for the disease need to be established. Once these risk factors are known, a cost benefit analysis can be performed, to provide insight into the cost saving implications of identifying these risk factors in patients before the onset of disease, or before the disease progresses to a severe level.

If we are able to better recognise risk factors for IPJ osteoarthritis, this information can be used to inform shared decision making between clinicians and patients. Such shared decision making might focus around strategies to modify risk factors, aiming to prevent the disease onset, or decrease the chance of the disease becoming more severe (56). Shared decision making could also be used in deciding how to treat the symptoms of the disease. In particular, this might focus on the treatment of severe or progressive IPJ osteoarthritis, stratifying a patient's risk of requiring invasive treatment, such as surgical intervention. In the surgical management of knee and hip osteoarthritis, shared decision-making between clinicians and patients has been shown to increase the confidence of patients at appointments, and the satisfaction of surgeons (114). Therefore, it is likely that if shared decision-making techniques can be used in the management of IPJ osteoarthritis, patient and clinician outcomes in managing the disease could increase.

Finally, identifying people at increased risk of developing IPJ osteoarthritis will enable their recruitment into randomised controlled trials. This is recognised to be particularly important, following the results from the Hydroxychloroquine Effectiveness in Reducing Symptoms of Hand Osteoarthritis randomised trial (115). The trial aimed to assess the effectiveness of hydroxychloroquine in reducing the symptoms of hand osteoarthritis. The results found hydroxychloroquine was no more effective than a placebo, yet the authors suggested this might have been because the study inclusion criteria did not recruit patients with severe enough disease (115). Guidelines surrounding the clinical trials for the pharmacological treatment of hand osteoarthritis recommend recruiting patients who already have the disease (116), and in the case of the hydroxychloroquine trial, this might mean people who are recruited to the trial are most likely to benefit from treatment with hydroxychloroquine (115). Therefore, in the future, if it were possible to identify people who are at risk of severe hand osteoarthritis (the most appropriate study participants) it would enable targeted recruitment of such people to similar trials.

1.7.1 Risk factors for incident versus the progression of osteoarthritis

It is possible that different risk factors exist for incident compared to the progression of osteoarthritis. Again, most of this evidence comes from studies of the lower limb, and in particular of the knee. Epidemiological data showing that the number of knee replacement surgery is lower than the number of people with incident knee osteoarthritis suggests that in only a proportion of people with knee osteoarthritis do the symptoms become severe enough to warrant arthroplasty, and instead, the disease can remain stable or indolent in some patients (117-121). Similarly, within patients with hip osteoarthritis, a systematic review identified groups of patients which had more rapidly progressive disease, such as those with atrophic bone or migration of the femoral head (122).

These studies suggest there are groups of patients with osteoarthritis which progresses, and other groups of patients who have stable disease that do not progress. In the hands, few studies have assessed risk factors for incident osteoarthritis separately to prognostic factors for the progression of the disease. However, it is recognised that not all patients with hand osteoarthritis will have progressive disease, as not all patients report a deterioration in their symptoms, nor require invasive management. To address these possible differences, this thesis will assess risk factors for incident IPJ osteoarthritis separately to prognostic factors for the progression of IPJ osteoarthritis.

1.7.2 Known risk factors for osteoarthritis

The aetiology of osteoarthritis can be classified into either intrinsic or extrinsic risk factors, and modifiable or non-modifiable risk factors. Most of the evidence for osteoarthritis risk factors comes from studies of the lower limbs, where injury and obesity have been identified as important risk factors (123, 124). However, in the hands, and particularly the IPJs, the relationship between injury and osteoarthritis has not yet been well studied. Concerning obesity, the relationship between obesity and hand osteoarthritis, particularly in the IPJs, shows conflicting evidence. This might be because the hands are not weight-bearing joints, though the IPJs can be considered to be load-bearing joints, due to the traction of tendons across these joints. This means load might be distributed differently across the IPJs in particular. Unlike osteoarthritis in the lower limb, the incidence of hand osteoarthritis peaks in perimenopausal women, and hand osteoarthritis is more prevalent in women than men (26, 32). This suggests that female hormonal factors might play a role in the development of hand osteoarthritis, unlike in osteoarthritis at other joints (125).

<u>Injury as a risk factor for hand osteoarthritis</u>

Joint injury can be caused by intra-articular fractures, by direct injuries to the menisci in the knee, and from injury to ligaments surrounding the joint (126). Resulting damage to the articular cartilage is difficult to repair, as this cartilage is avascular. If articular cartilage damage is associated with an underlying subchondral bone fracture, there is some chondral repair, though the mechanical properties of the newly formed cartilage are different to those of the native cartilage (126). If there is only isolated articular cartilage damage, there is often no repair, and, instead, there is a permanent defect in the surface of the cartilage (126).

The damaged cartilage leads to a change in force distribution across the joint. This is particularly important in the lower limb joints, which are all load bearing joints. Over time, this leads to the development of osteoarthritis, often termed post-traumatic osteoarthritis. In the knee, a systematic review and meta-analysis assessing risk factors for the incidence of radiographic knee osteoarthritis (defined as KL ≥2), identified 16 studies which reported on this association (127). Of these 16 studies, 14 found previous injury was an important risk factor for the incidence of radiographic knee osteoarthritis, with the meta-analysis showing a 3.9 times increased odds in people with a history of knee injury compared to those without such a history (127).

However, in the joints of the hands, which are not weight bearing, the development of post-traumatic osteoarthritis has been less frequently studied. To my knowledge, there is currently only one study which has investigated whether fracturing a finger is a risk factor for incident IPJ osteoarthritis (128). This was investigated by assessing the relationship between self-reported digit fracture with both radiographic DIPJ osteoarthritis (defined using the OARSI atlas) and with Heberden's nodes (128). The results showed a 2.4 times increased odds of DIPJ osteoarthritis in participants with a history of digit fracture, though no association with Hebderden's nodes (128). However, the analysis did not adjust for occupation, age, or sex, which might themselves be risk factors for IPJ osteoarthritis. Additionally, the authors noted that use of a self-reported questionnaire to capture a history of fracture had a high potential for mis-classification, and as such might not have correctly captured all participants with the exposure. Therefore, further studies, such as those in populations in which the risk of finger fracture is high, should be conducted to further understand the importance of injury in the development of IPJ osteoarthritis.

In this thesis, this will be investigated in a population of cricketers, in whom the risk of hand injury is considered to be particularly high (129).

Obesity as a risk factor for hand osteoarthritis

The evidence for obesity as a risk factor of osteoarthritis comes from the knee in particular. As the prevalence of obesity worldwide increases, there has been an increased focus on the implications to degenerative musculoskeletal disease, such as osteoarthritis (130). The pathology of obesity-related osteoarthritis is thought to be multi-factorial, including damage to articular cartilage from increase joint loading, altered biomechanics (including differences in step width, stride length, an increase in standing, and different biomechanics when standing from seating, in obese individuals (131)), and a low grade inflammatory state which may lead to joint inflammation (132, 133).

In the systematic review and meta-analysis assessing risk factors for the incidence of radiographic knee osteoarthritis (defined as KL ≥2), 36 studies which reported on obesity were identified (127). The random-effects pooled odds ratio in the meta-analysis reported a two to three times increased odds of radiographic knee osteoarthritis in people who were either overweight, obese, or overweight or obese, compared to those with normal body weight (127).

In the hands, obesity is unlikely to result in such a large biomechanical change, as the hands are do not bear load during walking or standing. However, it is possible that inflammatory joint changes due to obesity might play a role in hand osteoarthritis. In studies investigating the role of increased body mass index (BMI) with incident IPJ osteoarthritis, mixed evidence has been found for radiographic IPJ osteoarthritis, whilst an association has been found for both radiographic symptomatic and symptomatic IPJ osteoarthritis (128, 134-140).

Female hormonal factors as risk factors for hand osteoarthritis

The incidence of hand osteoarthritis is known to be highest in middle aged women, around the peri-menopausal age (26). This suggests that hand osteoarthritis might be associated with the onset of menopause.

A systematic review of trials assessing the effects of oophorectomy and oestrogen administration in animal models showed that oophorectomy was associated with cartilage degeneration, whilst oestrogen receptor modulators given after oophorectomy were protective for such degeneration (141). In humans, the role of female hormonal factors, such as oestrogen, are much harder to study. Studies assessing the frequency of hand osteoarthritis, in all hands joints and in DIPJs separately to other joints, have shown mixed effects for the association between the use of hormone replacement therapy with osteoarthritis (125). Therefore, though female hormonal factors may play a role in the pathogenesis of osteoarthritis in hand joints, the exact mechanism still remains unclear.

Given this paucity of research surrounding the aetiology of hand, and particularly IPJ osteoarthritis, this thesis will aim to develop a better understanding of risk factors for IPJ osteoarthritis. In patients, it is also likely that a combination of multiple potential risk factors are present, and the effect of an individual risk factor might also be influenced by the presence or absence of other risk factors. In the presence of multiple risk factors, the overall risk of a disease outcome can be estimated using prediction modelling (for new onset disease) or prognostic modelling (for change in disease status in a patient who already has the disease (for example, progression of a disease)). Prediction or prognostic modelling is a mathematical process, through which there is statistical analysis of collected data to estimate a future disease outcome. It is used to model disease outcomes in patients, and provides insight into the association between the disease outcome the multiple risk factors, but does not infer causation.

1.8 Aim of the thesis

The overall aim of this thesis was to identify risk factors associated with incident IPJ osteoarthritis, and identify prognostic factors associated with the progression of IPJ osteoarthritis.

1.8.1 Objectives

The objectives of this thesis were to:

1) Identify what is already known in the literature about risk factors and prognostic factors for IPJ osteoarthritis.

   1a) Identify risk factors and prognostic factors for IPJ osteoarthritis which surgeons recognise as being important in clinical practice.

2) Understand the role of a combination of risk factors in predicting incident IPJ osteoarthritis

3) Understand the role of a combination of prognostic factors in predicting the progression of IPJ osteoarthritis

4) Explore the incidence, pattern, nature and cause of hand injury in an at risk group, and assess the potential relationship between hand injury and osteoarthritis

1.8.2 Structure of the thesis

In order to answer the objectives above, I performed:

Chapter 2: Systematic reviews of the literature for a) risk factors for incident IPJ osteoarthritis, and b) prognostic factors for the progression of IPJ osteoarthritis. Data was also extracted on the diagnostic criteria used in the literature.

Chapter 2: Delphi studies of hand surgeons nationally, to assess a) risk factors they considered important for incident IPJ osteoarthritis, and b) prognostic factors they considered important for the progression of IPJ osteoarthritis, in clinical practice.

Chapter 3: Prediction modelling to develop a risk calculator for incident IPJ osteoarthritis, in middle-aged women in the UK, the population in which the incidence of hand osteoarthritis is highest.

Chapter 4: Prognostic modelling to assess the risk for the progression of IPJ hand osteoarthritis across an increasing number of joints, first in middle-aged women in the UK and then in both men and women in the USA.

Chapter 5: A study of routinely collected data was performed to investigate the type, severity, and cause of hand injury in a population of cricketers – a group in whom the prevalence of hand injury is known to be high. A second study was then performed to assess the relationship between injury with osteoarthritis in current and former (retired) cricketers.

Chapter 6: A summary of the main findings in this thesis and the clinical implications, and important limitations. Proposed research priorities for the future are also discussed.

2 CHAPTER 2: SYSTEMATIC REVIEWS AND DELPHI STUDIES

2.1 Chapter Aims

This chapter consists of two parts. Firstly, this chapter will ascertain the robustness of existing knowledge of risk factors for the incidence and progression of hand IPJ osteoarthritis, and classification criteria, answered through systematic reviews of the literature. This chapter will then assess whether there is consensus between clinicians in which important risk factors they identify in clinical practice, answered through Delphi studies of hand surgeons nationally.

2.2 Study 1: Systematic Reviews

2.2.1 Introduction

Identifying risk factors for the incidence of IPJ osteoarthritis can be difficult, as it is likely that the disease process is multi-factorial, with possible interactions between different risk factors, which themselves modify the overall risk of osteoarthritis developing. Additionally, identifying the exact onset of IPJ osteoarthritis is also difficult, as imaging, such as through plain film radiographs, is often taken after prolonged time intervals, and both symptoms and clinical signs may vary both within and between patients. Therefore, the presence of IPJ osteoarthritis is often studied.

Similarly, identifying prognostic factors for the progression of IPJ osteoarthritis can be complex, as the disease itself is considered to be chronic and progressive. It is possible that outside of the natural course of the disease, there are both patient-specific and external prognostic factors which can also affect the progression of the disease over time. This progression, a quantifiable change in the disease over time, is often referred to as the prognosis of the disease (142).

Identifying a risk or prognostic factor for a disease has historically been performed by investigating the association between a possible risk or prognostic factor and a disease outcome. The investigation itself is hypothesis driven, and this type of study is termed a phase 1 prognostic study

(143, 144). Phase 1 studies are therefore useful in generating hypotheses. However, it is recognised that often there are confounding factors which might act along these pathways, and therefore analyses which adjust for these confounding factors are termed phase 2 studies (143, 144). In a disease such as IPJ osteoarthritis, which is likely to have multiple risk or prognostic factors, identifying risk or prognostic factors from phase 1 and phase 2 studies can help to inform these complex pathways. The results can also be used to inform phase 3 studies, which assess multiple risk or prognostic factors for a disease together, such as through a prediction or prognostic model (143, 144).

2.2.1.1 Objectives

The objectives were to perform systematic reviews to identify risk factors for the presence of IPJ osteoarthritis, and prognostic factors for the progression of IPJ osteoarthritis, from the existing literature. As data extraction proceeded, it became clear there was no clear consensus definition for incident or progressive IPJ osteoarthritis. Therefore, the secondary objectives of the systematic reviews were to identify classification criteria used to describe the presence of IPJ osteoarthritis, and the progression of IPJ osteoarthritis, from the existing literature.

2.2.2 Methodology

Both systematic reviews used the same methodology, as listed below. However, study exclusion/ inclusion and data extraction was specific to each systematic review.

2.2.2.1 Reporting Guideline and Registration of reviews

The reporting of these reviews follows the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) statement (145). Both reviews were prospectively registered on PROSPERO (incident IPJ osteoarthritis: CRD42019116782, the progression of IPJ osteoarthritis: CRD42019121034) (146).

2.2.2.2 Search Strategy

The search strategy was built with the assistance of a specialist health-care librarian from the Knowledge Centre, Bodleian Libraries. Search terms relating to hand/fingers, osteoarthritis, incidence/ progression were used (search terms have been published and are available online through the following references (147, 148)). Four electronic databases were searched: Medline by Ovid, Embase by Ovid, Scopus, the Cochrane library. The search was initially conducted on 17th October 2018 and updated on 19th February 2020. Duplicates were removed and all articles imported into Rayyan QCRI Tool (149) for screening. Study titles and abstracts were screened independently by two groups of reviewers (for the review assessing risk factors for the presence of IPJ osteoarthritis: Group 1: myself (KS), Group 2: JCEL and HC; for the review assessing prognostic factors for the progression of IPJ osteoarthritis: Group 1: KS, Group 2: JCEL and XY). Any articles with insufficient information in the title or abstract were referred for full text review. The reference list of any eligible study was also assessed for additional papers. For any articles lacking full text, the authors were contacted directly (with a four-month return policy for the review assessing risk factors for the presence of IPJ osteoarthritis, and a two-month return policy for the review assessing prognostic factors for the progression of IPJ osteoarthritis). Any lack of agreement between the reviewer groups was discussed at a consensus meeting, with unresolved disagreement resolved through discussion with another independent reviewer (SRF).

2.2.2.3 Study eligibility criteria

The studies were assessed for inclusion in each review separately. Included studies must have investigated a potential risk factor and its association with the outcome, in comparison to participants without exposure to the risk factor. Studies must have specified the classification criteria for IPJ osteoarthritis (radiographic/ radiographic symptomatic/ symptomatic/ clinical signs/ multiple classification criteria), and measured IPJ disease separate to that at the first CMCJ. A time delay must have been present between exposure to the risk factor and the measurement of osteoarthritis (142). However, cross-sectional studies were included if exposure to the risk factor was historical and stable over time.

Case reports were excluded; and conference abstracts were also excluded as they are thought to have variable accuracy, information, and reliability of data (150, 151). Letters to the editor were examined at full text review to assess whether they were produced in the context of original studies. Those which were, were used to inform the inclusion of the original studies in our reviews, as such letters could contain additional, important information (150, 152). Studies of children were excluded, to prevent the analysis of juvenile arthritis. Studies of inflammatory and erosive arthritis were also excluded, as these are considered to be different disease types. Any studies in animals, cells, or cadavers were excluded. Genetic risk factors were not assessed in these reviews, as they are poorly described by risk and prognostic factor studies.

2.2.2.4 Data extraction

Data was extracted by one reviewer (KS) for input into a Microsoft Excel document. Another independent reviewer (for the review assessing risk factors for the presence of IPJ osteoarthritis: HC; for the review assessing risk factors for the progression of IPJ osteoarthritis: XY) cross-checked the data. Extracted data included information about the study (for example, design), study participants (for example, sex or gender, age), risk/ prognostic factor, osteoarthritis classification, effect measure, and the effect outcome. Any results reported at multiple time points were extracted. Any additional data required was requested from the authors (with a four-month return policy for the review assessing risk factors for the presence of IPJ osteoarthritis, and a two-month return policy for the review assessing prognostic factors for the progression of IPJ osteoarthritis).

During data extraction it became clear that there was no consensus in the classifications used for the presence of IPJ osteoarthritis or its progression. Therefore, data was extracted for the classifications used for IPJ osteoarthritis. Data was extracted separately for radiographic, radiographic symptomatic, and symptomatic IPJ osteoarthritis.

<u>Subgroup analysis</u>

Data was extracted separately for all IPJs, DIPJs only, and PIPJs only.

2.2.2.5 Risk of bias assessment

Risk of bias assessment was performed by two reviewers independently (for the review assessing risk factors for the presence of IPJ osteoarthritis: KS and HC; for the review assessing risk factors for the progression of IPJ osteoarthritis: KS and XY). Any lack of agreement between the reviewers was discussed at a consensus meeting, with unresolved disagreement addressed through discussion with another independent reviewer (SRF).

The Quality in Prognostic Studies (QUIPS) Tool was used to assess risk of bias, developed by the Cochrane Prognosis Methods Group (153). The QUIPS tool contains six domains: 1) Study participation, 2) Study attrition, 3) Prognostic factor measurement, 4) Outcome measurement, 5) Study confounding, 6) Statistical analysis and reporting. However, confounders themselves are often considered to be prognostic factors, and therefore we excluded this domain (154). Each domain contains multiple items which are judged for adequacy in the study ('yes/ no/ unsure'). If information pertaining to a particular item is lacking in a study, the item is judged as 'no' or 'unsure'. All of the items are then assessed in combination to rate the risk of bias for the relevant domain ('high/ moderate/ low'). However, the QUIPS tool does not use a quantitative method to determine the risk of bias for a domain, and therefore such a method was developed by the reviewers who assessed the risk of bias (KS, HC, XY) (the modified QUIPS tool has been published and is available online through the following references (147, 148)):

- If more than half of the items are 'no/unsure', risk of bias is high.
- If all items are 'yes', risk of bias is low.

- If any other combination of items, risk of bias is moderate.

The QUIPS tool also does not provide guidance on how the overall risk of bias for a study should be determined. Therefore, common methods used in the literature were applied:

- If at least one domain was of high risk of bias, the overall risk of bias was high (153, 155-157)
- If at least three domains were of moderate risk of bias (none with high risk of bias), the overall risk of bias was moderate (153, 155)
- If all domains were of low risk of bias, or if less than three domains were of moderate risk of bias, the overall risk of bias was low (156, 158, 159)

2.2.2.6 Data analysis and Best evidence synthesis

Data was analysed separately for each review. If study characteristics, risk factors assessed and definitions of osteoarthritis were homogenous, a meta-analysis was considered to pool data, and quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation framework (160).

If studies were heterogenous in terms of study participants, risk or prognostic factor, or outcome (classification criteria for IPJ osteoarthritis), a qualitative summary was used. The association between a potential risk factor and IPJ osteoarthritis was described as either 'a risk factor (i.e.- positive effect measure)/ not a risk factor (i.e.- protective)/ conflicting evidence (i.e.- both positive and negative effect measures)'. A best evidence synthesis method was used to summarise the consistency and strength of the evidence for the association (122, 161-163) (Table 2.1). The methodology was applied sequentially and used to assess both intra-study and inter-study risk factors.

Table 2.1: Best Evidence Synthesis

Consistency of evidence:	**Consistent** (≥75% of studies with association in the same direction)	**Inconsistent** (<75% of studies with association in the same direction)
Strength of evidence:	**a) Strong** (>2 studies with low risk of bias)	
	b) Moderate (1 study with low risk of bias & 1 other study OR- >2 studies with moderate/ high risk of bias)	
	c) Limited with low risk of bias (1 study with low risk of bias)	
	d) Limited (1 or 2 studies with moderate/ high risk of bias)	

2.2.3 Results

2.2.3.1 Search results

When combining the results from the 2018 and 2020 searches, 25,739 studies were identified. 12,393 of these were duplicates and removed (Figure 2.1; results from the 2018 search only have been published and are available online through the following reference (148)). Following the screening of reference lists, no further studies were included.

2.2.3.2 Risk factors for the presence of IPJ osteoarthritis

Search results and included studies

178 full texts were reviewed, and of these 18 studies were included in the systematic review (Figure 2.1) (128, 134-140, 164-173).

Characteristics of included studies

Of the 18 studies, four were prospective cohort studies, (135, 138, 165, 169) whilst 11 were cross-sectional studies (128, 134, 136, 137, 139, 140, 166-168, 170, 172), and three were case-control studies (164, 171, 173) (Table 2.2). Five studies assessed only women (137, 138, 140, 166, 167). Not all of the studies reporting the mean age of participants, but from those which did, the youngest mean age was 39.2 (standard deviation (SD): 3.6) years (171), and the oldest age was 72 (SD: 5) years (172).

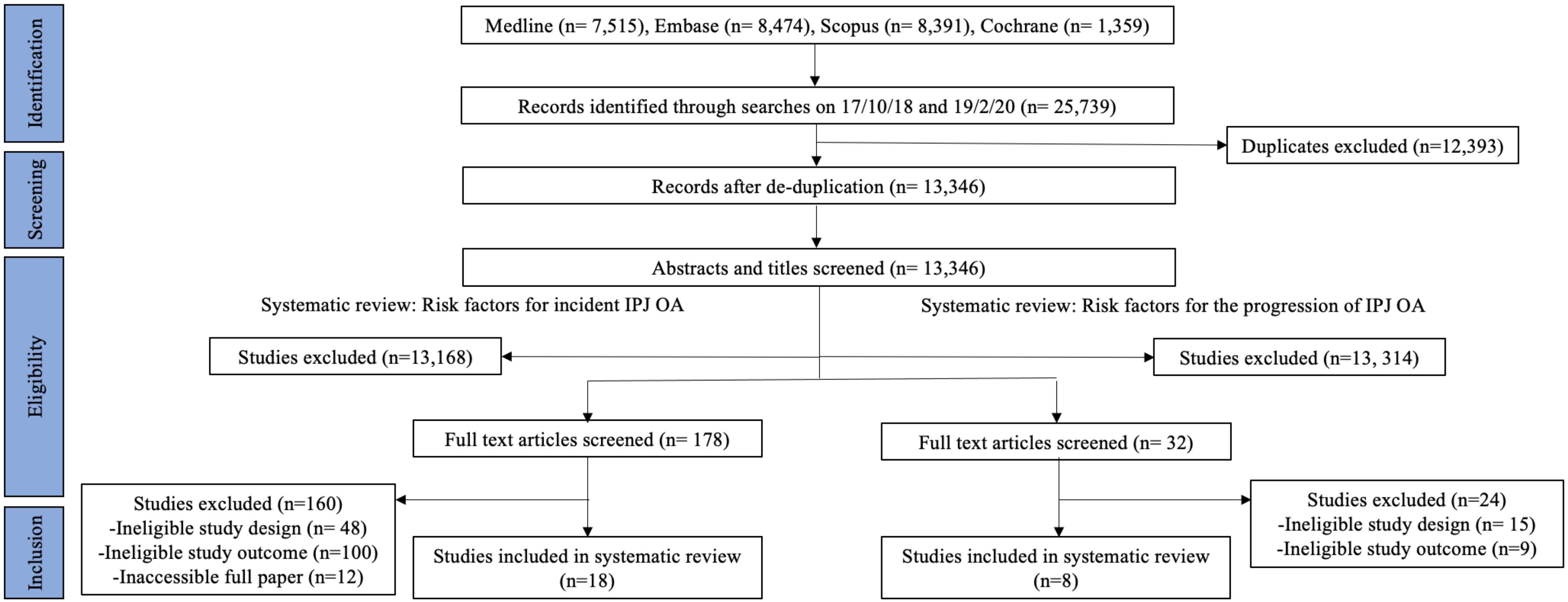

Figure 2.1: Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart of studies included in the systematic reviews

IPJ: Interphalangeal joint; OA: Osteoarthritis

Table 2.2: Studies included in the systematic review assessing risk factors for the presence of IPJ osteoarthritis

Study	Population	Type of study	Age (years) (Mean)	Female (%)	Eligibility criteria (Inclusion Criteria; Exclusion Criteria)	N= at baseline, n= at follow up	Classification criteria for IPJ OA	Potential risk factor assessed
Lehto et al (164)	Cases: Dentists registered with Turku dental society, Controls: Finish	Case control	NR	Cases: 68.0 Controls: 52.9	Cases: Practising dentistry for ≥10 years, Controls: NR; Cases: >69 years old, Controls: NR	Cases: 136, Controls: 940, n/a	Outcome 1: Total number of IPJs with KL grade ≥2* Outcome 2: KL grade ≥2 in DIPJ of the index finger used for pinch-power	Dental occupation in men, Dental occupation in women, Pinch power- Stronger
Chaisson et al (165)	American population	Prospective cohort	M: 54 F: 36	61.8	No hand OA at baseline xrays; Rheumatoid arthritis, Missing grip strength data	2547, 453	Total number of IPJs with KL grade ≥2 at follow-up from 0/1 at baseline of the right hand only *	Grip strength in men- Higher, Grip strength in women- Higher
Cvijetiae et al (134)	Swiss population	Cross sectional	M: 63.6 F: 63.6	50.2	NR; Rheumatoid arthritis, Gout, Amputated fingers or limbs	610, n/a	KL grade ≥2 (no further information given) *	Age in men- Older, Age in women- Older, BMI in men- Higher, BMI in women- Higher, Menopause years- Longer, Blood pressure (systolic) in men- Higher, Blood pressure (diastolic) in men- Higher, Blood pressure (systolic) in women- Higher, Blood pressure (diastolic) in women- Higher, Smoking
Yoshida et al (166)	Japanese and American elderly women	Cross sectional	NR	100	Women, Aged >70 years; NR	Japan: 157, USA 655, n/a	KL grade ≥2 of the second and third fingers *	Japanese ethnicity in women
Jones et al (128)	Tasmanians with hand OA or relative with hand OA	Cross sectional	M: 53.2 F: 57.0	66.7	Hand OA and one living relative with hand OA; NR	522, n/a	Outcome 1: Presence of JSN or OP, as defined by the Altman atlas, in ≥1 DIPJ Outcome 2: Sum score of JSN and OP, as defined by the Altman atlas, in all DIPJs	BMI- Higher, BMI- Lower, History of finger fracture, Mechanical stress during work, Physical activity
Cooley et al (167)	Tasmanian with hand OA	Cross sectional	Index: 79 Family: 51	100	Diagnosis of hand OA and ≥1 living relative with hand OA, >34 years old; NR	348, n/a	Outcome 1: Presence of JSN or OP, as defined by the Altman atlas, in ≥1 DIPJ Outcome 2: Sum score of JSN and OP, as defined by the Altman atlas, in all DIPJs	Breastfed ever, Hysterectomy, Menarche age- Older, Menstruation years- Longer, Menopause age- Older, Number of children- Higher, Oral contraceptive use, Oral contraceptive duration- Longer

Haara et al (135)	Finnish adults with musculoskeletal disease	Prospective cohort	NR	56.5	Age over 29 years, History/ symptoms/ findings which suggest musculoskeletal disease; NR	3595, 2698	KL grade ≥2 in ≥2 symmetrical DIPJs	BMI- Higher, Education- longer, Female gender, Physical exertion at work, Smoking
Kessler et al (136)	Germans	Cross sectional	NR	NR	Bilateral hand radiographs; NR	639, n/a	Using the Kessler hand scale, Altman JSN grade ≥2 in ≥2 IPJs or JSN grade 1 with sclerosis or OP grade ≥2 in ≥2 IPJs	BMI- Higher, Diabetes, Female gender, Hypertension, Physical exertion at work
Kalichman et al (168)	Russians	Cross sectional	M: 46.1 F: 47.9	47.2	NR; NR	1245, n/a	KL sum score for IPJs *	Age in men- Older, Age in women- Older, Female gender
Solovieva et al (137)	Finish residents	Cross sectional	54	100	Resident in Helsinki or neighbouring cities, Aged 45 – 63 years; Incomplete questionnaire	291, n/a	Outcome 1: KL grade ≥2 in ≥1 IPJs; Outcome 2: KL grade ≥2 in ≥1 IPJs of ring and little fingers	Age in women- Older, BMI in women- Higher, Family history of Heberden's nodes in women, Mechanical stress during work in women
Szoeke et al (138)	Australian women	Prospective cohort	49.66	100	Menses in preceding 3 months, Born in Australia, Aged 45-55 years, Living in Melbourne, participants whom attended at baseline and follow up; Oral contraceptives, Hormone replacement	224, 224	Outcome 1: Altman (83) OP grade ≥2 in ≥1 IPJ *; Outcome 2: Altman (83) JSN grade ≥2 in ≥1 IPJ *	Age in women- Older, BMI in women- Higher, Hormonal therapy- no use, Physical activity in women, Smoked (never) in women
Dahaghin et al (139)	Dutch adults	Cross sectional	66	58.2	Live in Ommoord, Age >54 years, Available for 6 year follow-up; NR	3585, n/a	KL grade ≥2 in ≥1 IPJ *	BMI- Higher
Ding et al (140)	Finnish people	Cross sectional	Dentists: 54 Teachers: 54	100	NR; Rheumatoid arthritis diagnosed by a doctor	532, n/a	KL grade ≥2 in ≥1 DIPJ	BMI in women- Higher
Biermasz et al (169)	People with acromegaly	Prospective cohort	56.8	33	In long-term remission of acromegaly; Diagnosed before 1986 when IGF-1 assay was not available	67, NR	Sum KL score in IPJs *	IGF-1- Higher
Hoeven et al (170)	Dutch adult	Cross sectional	NR	57.1	Age ≥55 years, Living for ≥1 year in Ommoord district; Rheumatoid arthritis on hand xrays, fractures on hand xrays	5614, n/a	KL grade ≥2 in ≥1 IPJs *	Atherosclerosis
Fu et al (171)	Chinese adults	Case control	Cases: 39.2 Controls: 38.7	Cases: 21.3 Control: 23.5	NR; NR	Cases: 127, Controls: 311, n/a	Outcome 1: OARSI OP grade ≥1 in ≥1 IPJ of right hand *; Outcome 2: OARSI OP grade ≥3 in ≥1 IPJ of right hand *; Outcome 3: OARSI JSN grade ≥1 in ≥1 IPJ of right	Adult Kashin Beck Disease

							hand *; Outcome 4: OARSI OP grade ≥3 in ≥1 IPJ of right hand *; Outcome 5: KL grade ≥2 in ≥1 IPJ of right hand *; Outcome 6: KL grade 4 in ≥1 IPJ of right hand *	
Cho et al (172)	Japanese elderly people	Cross sectional	72	57	Age ≥65 years, Living in Seongnam; History of hand trauma, Hand deformity causing poor quality xrays, No hand xrays available	692, n/a	KL grade ≥2 in ≥1 IPJs*	Female gender
Gregson et al (173)	Cases: Person with hand OA Controls: Unaffected first degree relatives or spouses	Case control	Cases: 61.1 Controls: 54.3	Cases: 74.5 Controls: 45.9	NR; <18 years old, pregnant, unable to provide written consent	Cases: 314, Controls: 183, n/a	Outcome 1: Altman OP grade ≥1 in ≥1 DIPJ of dominant hand; Outcome 2: Altman OP grade ≥ 2in ≥1 DIPJ of dominant hand; Outcome 3: Altman JSN grade ≥1 in ≥1 DIPJ of dominant hand; Outcome 4: Altman JSN grade ≥2 in ≥1 DIPJ of dominant hand; Outcome 5: Presence of sub-chondral sclerosis, as defined by the Altman atlas, in ≥1 DIPJ of dominant hand; Outcome 6: Presence of malalignment, as defined by the Altman atlas, in ≥1 DIPJ of dominant hand	Bone mass- Higher

BMI: Body mass index; DIPJ: Distal interphalangeal joint; F: Females; IGF-1: Insulin- like Growth Factor 1; IPJ: Interphalangeal joint; JSN: Joint space narrowing; KL: Kellgren Lawrence; M: Males; N/A: Not applicable; NR: Not recorded; OA: Osteoarthritis; OARSI: Osteoarthritis Research Society International (synonymous with the Altman atlas); OP: Osteophyte; PIPJ: Proximal interphalangeal joint; Xrays: Plain film radiographs
*DIPJs and PIPJs assessed separately

Risk of bias

Risk of bias was found to be high in eight studies (128, 135, 164, 165, 167-170), moderate in three studies (134, 138, 172), and low in seven studies (136, 137, 139, 140, 166, 170, 173) (Table 2.3). The first domain, 'Study participation' was of high risk of bias in two studies which did not describe the source populations and did not indicate whether ≥80% of eligible individuals were included (128, 171). The second domain, 'Study attrition', was of high risk of bias in two studies as there was no description of attrition (135, 164). The third domain, 'Prognostic factor measurement' was found to be of high risk of bias in three studies, as two of these studies did not describe the prognostic factors (167, 168), and one study converted a continuous variable to categorical (169). Converting continuous variables into categorical is known to decrease the granularity of data, can lead to arbitrary cut-off points, and is not representative of the natural state of the data (174). The 'Outcome measure' was assessed in the fourth domain and was of high risk of bias in only one study, due to a lack of blinding of the assessor (165). No studies were found to have high risk of bias in the fifth domain, 'Statistical analysis and Reporting'.

Table 2.3: Risk of bias for included studies in systematic review assessing risk factors for the presence of IPJ osteoarthritis

Study	Biases*					Overall risk of bias
	1	2	3	4	5	
Lehto et al (164)	Moderate	High	Moderate	Low	Moderate	**High**
Chaisson et al (165)	Moderate	Moderate	Low	High	Moderate	**High**
Cvijetiae et al (134)	Moderate	Low	Low	Moderate	Moderate	**Moderate**
Yoshida et al (166)	Moderate	Low	Low	Moderate	Low	**Low**
Jones et al (128)	High	Low	Moderate	Moderate	Low	**High**
Cooley et al (167)	Moderate	Low	High	Moderate	Low	**High**
Haara et al (135)	Low	High	Moderate	Low	Low	**High**
Kessler et al (136)	Moderate	Low	Moderate	Low	Low	**Low**
Kalichman et al (168)	Moderate	Low	High	Moderate	Moderate	**High**
Solovieva et al (137)	Moderate	Low	Moderate	Low	Low	**Low**
Szoeke et al (138)	Moderate	Low	Moderate	Moderate	Low	**Moderate**
Dahaghin et al (139)	Moderate	Low	Moderate	Low	Low	**Low**
Ding et al (140)	Moderate	Low	Moderate	Low	Low	**Low**
Biermasz et al (169)	Moderate	Low	High	Low	Low	**High**
Hoeven et al	Moderate	Low	Moderate	Low	Low	**Low**
Fu et al (171)	High	Low	Moderate	Moderate	Moderate	**High**
Cho et al (172)	Moderate	Low	Moderate	Moderate	Moderate	**Moderate**
Gregson et al (173)	Moderate	Moderate	Low	Low	Low	**Low**

*Biases from Modified Quality in Prognosis Studies (QUIPS) Tool. Domains assessed: 1) Study participation; 2) Study attrition; 3) Prognostic factor measurement; 4) Outcome measure; 5) Statistical analysing and Reporting

Classification criteria for the presence of IPJ osteoarthritis

Classification criteria was heterogenous across the 18 studies (128, 134-140, 164-173). Radiographic classification criteria was used by all studies, of which a version of the KL atlas (79, 80, 175) was most often used, followed by the Altman (OARSI) atlas (83, 84). One study also included a radiographic symptomatic criteria, classifying the presence of IPJ OA using both the KL atlas (KL grade ≥2) with the presence of 'mild' pain in ≥1 DIPJ over the last 30 days (140). Two studies additionally included classification criteria based on clinical signs, describing the total number of DIPJs with Heberden's nodes (128), or the presence of Heberden's nodes in at least one DIPJ (167).

Risk factors for the presence of radiographic IPJ osteoarthritis

In total, 49 potential risk factors were assessed, with eight being identified as risk factors (Table 2.4). Effect measures and outcomes were heterogenous across studies (effect measures and outcomes have been published and are available online through the following reference (148)). It was not possible to perform a meta-analysis due to the variety of effect measures used across studies.

Older age in women had moderate evidence as a risk factor. Four studies assessed older age in women as a potential risk factor (134, 137, 138, 168). All studies assessed age continuously, and three of the four studies measured IPJ osteoarthritis using the KL atlas (134, 137, 168), whilst one study used the Altman atlas (138). Within each study, there was consistent evidence for older age in women being a risk factor. In the subgroup analysis for DIPJ and PIPJ osteoarthritis separately, three studies assessed older age in women as a risk factor, with two studies using the KL atlas (134, 168), and one study using the Altman atlas (138). In each subgroup, older age in women was found to be a risk factor when the KL atlas was used diagnose osteoarthritis (134, 168), but not when the Altman atlas was used for diagnosis (138).

There was moderate evidence for female sex as a risk factor, across four studies, all which classified osteoarthritis using the KL atlas (135, 136, 168, 172). In the DIPJ subgroup analysis, all four studies were included, and the moderate evidence remained (135, 136, 168, 172). Whilst in the PIPJ subgroup analysis, two studies were included, and though both found an association between female sex and the incidence of PIPJ osteoarthritis, the evidence was limited due to both studies being of moderate/ high risk of bias (168, 172).

Family history of Heberden's nodes in women was found to be a risk factor for IPJ osteoarthritis with limited evidence in one low risk of bias study (137). The classification criteria used the KL atlas, with two different definitions, and therefore two outcomes. Both outcomes found an association. There was no subgroup analysis.

Adult Kashin-Beck disease (171), dental occupation in men (164), history of finger fracture (128), parity (167), and older age in men (134, 168) were all found to be risk factors for the incidence of IPJ osteoarthritis, with low evidence. All of these risk factors were assessed in one study only, with the exception of older age in men, which was assessed in two studies (134, 168). Adult Kashin-Beck disease was assessed in one study (171), which used eight classification criteria based on the Altman (OARSI) atlas, and three classification criteria based on the KL atlas. There was an association regardless of which classification criteria was used. However, this study was found to have a high risk of bias. In both the DIPJ and PIPJ subgroup analyses, the association remained. Dental occupation in men was found to have an association in one high risk of bias study, which used the KL atlas to diagnose DIPJ osteoarthritis only (164). History of finger fracture was also found to have an association in one high risk of bias study, which used the Altman atlas to diagnose DIPJ osteoarthritis only (128). Similarly, parity (yes versus no) was found have an association in one high risk of bias study, which used the Altman atlas to diagnose DIPJ osteoarthritis only (167). Older age in men was investigated across two studies, both which used the KL atlas for diagnosis of osteoarthritis, and both which found an association (134, 168). In the subgroup analyses, these associations remained for both the DIPJ and PIPJ.

Risk factors for the presence of radiographic symptomatic IPJ osteoarthritis

The only potential risk factor assessed was BMI in women (assessed in arbitrary categories) (140). This showed limited evidence as a risk factor in one low risk of bias study, which classified DIPJ osteoarthritis using the KL atlas, for being a prognostic factor (effect measures and outcomes have been published and are available online through the following reference (148)).

Risk factors for the presence of clinical IPJ osteoarthritis

In total, 14 potential risk factors were assessed for their association with clinical DIPJ osteoarthritis, across the two high/moderate risk of bias studies (128, 167) (Table 2.5) (effect measures and outcomes have been published and are available online through the following reference (148)). Each potential risk factor was assessed by one study only, and no associations were found (limited evidence).

Table 2.4: Potential risk factors assessed in the systematic review for the presence of radiographic IPJ osteoarthritis

Consistent (≥75% of studies with association in the same direction)		Inconsistent (<75% of studies with association in the same direction)
Risk factor	**Not a risk factor**	
Strong	**Strong**	Higher BMI[f,g] (128, 135, 136, 139), Higher BMI in men[b,j] (134)*, Higher IGF-1[f,k] (169)
Moderate Older age in women[f,k] (134, 137, 138, 168), Female sex[h] (135, 136, 168, 172)	**Moderate** Higher BMI in women[c,j] (137)* (134, 138, 140)	
Limited with low risk of bias Family history of Heberden's nodes in women (137)	**Limited with low risk of bias** Atherosclerosis in men[d,i] (170), Atherosclerosis in women[f,I] (170), Higher bone mass[d] (173), Diabetes[d] (136), Hypertension[d], Mechanical stress in women (137), Physical exertion at work[d] (135, 136)	
Limited Adult Kashin Beck disease[b,h] (171), Older age in men[b,h] (134, 168) Dental occupation in men[b] (164), History of finger fracture[b] (128), Parity[b] (167)	**Limited** Higher diastolic blood pressure in men[e,j] (134), Higher systolic blood pressure in men[e,j] (134), Higher diastolic blood pressure in women[e,j] (134), Higher systolic blood pressure in women[e,j] (134), Lower BMI[e] (135), Ever breastfed[e] (167), Dental occupation in women[e] (164), Longer education[e] (135), Higher grip strength in men[e,k] (165), Higher grip strength in women[e,j] (165), No use of hormonal therapy[f,j] (167), Hysterectomy[e] (167), Japanese ethnicity[j] (166), Older age at menarche[e] (167), Longer years of menstruation[e] (167), Older age at menopause[e] (167), Longer years of menopause[e,j], Mechanical stress during work[e], Higher number of children[e] (167), Oral contraception use[e] (167), Longer duration of oral contraception use[e] (167), Physical activity[e,j] (128, 138), Physical exertion in men[e] (135), Physical exertion in women[e] (135), Stronger pinch power[e] (164), Smoking[e] (128), Smoking in men[e,j] (128, 135), Smoking in women[e,j] (128, 135), Never smoked in women[e,j] (138)	

BMI: Body mass index; IGF-1: Insulin growth factor-1

*Mixed evidence within study, [a]DIPJ: Prognostic factor (moderate evidence), [b]DIPJ: Prognostic factor (limited evidence), [c]DIPJ: Not a prognostic factor (moderate evidence), [d]DIPJ: Not a prognostic factor (limited evidence with low risk of bias), [e]DIPJ: Not a prognostic factor (limited evidence), [f]DIPJ: Mixed evidence, [g]PIPJ: Prognostic factor (limited evidence with low risk of bias), [h]PIPJ: Prognostic factor (limited evidence), [i]PIPJ: Not a prognostic factor (limited evidence with low risk of bias), [j]PIPJ: Not a prognostic factor (limited evidence), [k]PIPJ: Mixed evidence

Table 2.5: Potential risk factors assessed in the systematic review for the presence of clinical IPJ osteoarthritis

Consistent (≥75% of studies with association in the same direction)		**Inconsistent** (<75% of studies with association in the same direction)
Risk factor	**Not a risk factor**	
Strong	**Strong**	
Moderate	**Moderate**	
Limited with low risk of bias	**Limited with low risk of bias**	
Limited	**Limited** Higher BMI (128), Ever breastfed (167), History of finger fracture (128), Hysterectomy (167), Mechanical stress during work (128), Older age at menarche (167), Longer years of menstruation (167), Older age at menopause (167), Higher number of children (167), Oral contraception use (167), Longer duration of oral contraception use (167), Parity (167), Physical activity (128), Smoking (128)	

BMI: Body mass index

2.2.3.3 Prognostic factors for the progression of IPJ osteoarthritis

Search results and included studies

32 full texts were reviewed, and of these eight studies were included in the systematic review (170, 176-182) (Figure 2.1).

Characteristics of included studies

All of the 8 studies were prospective cohort studies (170, 176-182) (Table 2.6). Three studies assessed only men (176-178), and five studies assessed men and women (170, 179-182). Five studies reported the mean age of participants (170, 179-182), and from those, the youngest mean age was 45.3 years in men and 49.7 years in women (181), and the oldest age was 67.5 years in men and 68.6 years in women (170).

Table 2.6: Studies included in the systematic review assessing risk factors for the progression of IPJ osteoarthritis

Study	Population	Age (years) (mean)	Female (%)	Eligibility criteria (Inclusion Criteria; Exclusion Criteria)	N= at baseline, n= at follow up	Classification criteria for IPJ OA	Potential risk factor assessed
Plato et al (178)	White middle class volunteers participated in the BLSA in the USA	NR	0	NR; NR	478 (NR)	Increase by ≥1 grade from the highest KL (79) grade at baseline in any DIPJ	Older age in men
Kallman et al (176)	White middle class volunteers who participated in the BLSA in the USA	NR	0	NR; Maximum KL score (4) at baseline (per patient); Not specified	177 (177)	Increase by ≥1 grade from the highest KL (79, 80) grade at baseline in any PIPJ	Older age in men
Busby et al (177)	White middle class volunteers who participated in the BLSA in the USA	NR	0	NR; Joints with KL score of 4 at baseline	386 (NR)	Outcome 1: Increase by ≥1 grade from the highest KL (80) grade at baseline in any IPJ (DIPJ and PIPJ assessed separately) Outcome 2: Increase in number of IPJs with KL (80) grade ≥2 (DIPJ and PIPJ assessed separately)	Older age in men
Kalichman et al (181)	Chuvashians; Village; Randomly recruited	Men: 45.3, Women: 49.7	52	NR; NR	263 (263)	Increase in number of IPJs with KL (80) grade ≥2 (DIPJ and PIPJ assessed separately)	Alcohol, Anthropometric features, Familial relationship, Gender (female), Older age in men, Older age in women, Smoking
Kalichman et al (182)	Chuvashians; Village; Randomly recruited	Men: 47.4, Women: 50.9	46	NR; Bone disease, Amenorrhoea, Hormone replacement therapy, Steroids	557 (513)	Increase by ≥1 grade in a cumulative KL [38] sum score (2^{nd}, 3^{rd} and 4^{th}' PIPJs)	Epiphyseal index (larger)
Hoeven et al (170)	Rotterdam	Men: 67.5, Women: 68.6	58	≥55 years, living for ≥1 year in Ommoord, Knee, hip, hand Xrays; No xrays, rheumatoid, fractures	5650 (2442)	Increase by ≥1 KL (79) grade in ≥1 IPJ, if ≥1 IPJ had KL(79) grade ≥2 at baseline (DIPJ and PIPJ assessed separately)	Atherosclerosis

Haugen et al (179)	USA; Hospital study sites	58.4	58	NR; Systemic inflammatory arthritis, Bilateral end stage knee OA, Inability to walk without aids, Contraindication to MRI	994 (994)	Increase by ≥1 grade in a cumulative Modified KL (80, 183) sum score (DIPJ and PIPJ assessed together)	Alcohol (higher intake), BMI (higher)- At age 25, BMI (higher)- Current, Smoking, Waist circumference (higher)
Marshall et al (180)	From CASHA & CASK cohorts; GP community	60.5	60	Age 50-69 years at baseline, Reported hand pain in last month; Inflammatory arthritis, All hand joints affected with KL≥2 at baseline, Deaths/ untraceable/ address unknown, Severe/ terminal illness	706 (388)	Outcome 1: Increase by ≥1 grade in a cumulative KL (184) sum score (DIPJ and PIPJ assessed together) Outcome 2: Increase in number of IPJs with KL (184) grade ≥2 (DIPJ and PIPJ assessed together)	BMI (higher)- Current, Diabetes type 2/ Impaired fasting glucose, Dyslipidaemia, Hypertension, Number of metabolic factors (higher)

BLSA: Baltimore Longitudinal Study of Aging; BMI: Body mass index; CASHA: Clinical Assessment Studies of the Hand; CASK: Clinical Assessment Studies of the Knee; DIPJ: Distal interphalangeal joint; GP: General Practice; IPJ: Interphalangeal joint; KL: Kellgren-Lawrence atlas; PIPJ: Proximal interphalangeal joint; N: Number at baseline; n: Number at follow-up; NS: Not specified; OA: Osteoarthritis; USA: United States of America; Xrays: Plain film radiographs

Risk of bias

Risk of bias was found to be high in seven studies (176-179, 181, 182), and moderate in one study (170) (Table 2.7). The first domain, 'Study participation' was of high risk of bias in four studies which did not describe the recruitment periods or places (176, 178, 179, 182). The second domain, 'Study attrition', was also of high risk of bias in four studies, due to response rates and reasons for losses to followup not being adequately reported, and <80% response rates being found (176, 178-180, 182). The third and fourth domains, were not found to be of high risk of bias in any study. The fifth domain, 'Statistical analysis and Reporting' was of high risk of bias in three studies, as the effect outcomes were not reported (only significance levels were reported) (177, 178, 181).

Table 2.7: Risk of bias for included studies in systematic review assessing prognostic factors for the progression of IPJ osteoarthritis

Study	**Biases***					**Overall risk of bias**
	1	**2**	**3**	**4**	**5**	
Plato et al (178)	High	High	Moderate	Moderate	High	**High**
Kallman et al (176)	High	High	Low	Low	Moderate	**High**
Busby et al (177)	Moderate	Moderate	Low	Moderate	High	**High**
Kalichman et al (181)	Moderate	Low	Moderate	Moderate	High	**High**
Kalichman et al (182)	High	High	Moderate	Low	Moderate	**High**
Hoeven et al (170)	Moderate	Low	Moderate	Low	Moderate	**Moderate**
Haugen et al (179)	High	High	Moderate	Moderate	Moderate	**High**
Marshall et al (180)	Moderate	High	Low	Moderate	Low	**High**

*Biases from Modified Quality in Prognosis Studies (QUIPS) Tool. Domains assessed: 1) Study participation; 2) Study attrition; 3) Prognostic factor measurement; 4) Outcome measure; 5) Statistical analysing and Reporting

Classification criteria for the progression of IPJ osteoarthritis

All studies used radiographic classification criteria based on the KL atlas only (79, 80, 170, 176-182) (Table 2.6). However, the classification criteria was heterogenous across the eight studies, and some studies used multiple classification criteria. The progression of IPJ osteoarthritis was defined as an increase in KL grade from the highest KL grade at baseline in three studies (176-178); as an increase in the number of IPJs with osteoarthritis (KL ≥2) from baseline in three studies (177, 180, 181); as an increase in cumulative KL grade from baseline in three studies (179, 180, 182); and as an increase in KL grade in at least one IPJ from baseline in one study (170).

Prognostic factors for the progression of radiographic IPJ osteoarthritis

A total of 18 potential prognostic factors were assessed. Potential prognostic factors were most commonly assessed in only one study, and those which were assessed in multiple studies could not be meta-analysed due to heterogeneity (effect measures and outcomes have been published and are available online through the following reference (147)). The results are presented using the best evidence synthesis approach. Overall, three prognostic factors were identified (Table 2.8).

Diabetes (yes versus no) was found to be a risk factor for IPJ osteoarthritis progression in one study with high risk of bias, and therefore the evidence was limited (180) (Table 2.8). In this study, two classification criteria were used to define osteoarthritis progression (Table 2.6): Increase by ≥1 grade in a cumulative KL sum score in all IPJs, and increase in number of IPJs with osteoarthritis (KL ≥2). When a complete case analysis was used for each classification criteria, an association was found, but when multiple imputation was used, an association was only found for the latter classification criteria. No subgroup analysis could be performed.

Larger finger epiphyseal index was investigated as a risk factor in men and in women in one high risk of bias study (182). Epiphyseal index was defined as the ratio between the total bone surface area and the bone surface area minus the widening of the phalanges at the IPJs, of the middle phalanges of the index, middle and ring fingers. The classification criteria was defined an increase by ≥1 grade in a cumulative KL sum score in PIPJs only. An association was found in both men and in women.

Table 2.8: Risk factors assessed in the systematic review for the progression of IPJ osteoarthritis

Consistent (≥75% of studies with association in the same direction)		**Inconsistent** (<75% of studies with association in the same direction)
Risk factor	**Not a risk factor**	
Strong	**Strong**	Older age in men[c,] (176-178, 181), Older age in women[a,f] (181)
Moderate	**Moderate**	
Limited with low risk of bias	**Limited with low risk of bias**	
Limited Diabetes/ Impaired fasting glucose **(180)**, Larger epiphyseal index in females[d] **(182)**, Larger epiphyseal index in males[d] **(182)**	**Limited** Higher alcohol intake[b,e] (179, 181), Anthropometric features[b,e] (181), Atherosclerosis[b,e] (170), Larger BMI- at age 35 years (179), Larger BMI- Current (179), Dyslipidaemia (180), Familial relationship[b] (181), Female sex (181), Hypertension (180), Higher number of metabolic factors (180), Larger waist circumference (179), Male sex (181), Smoking (179, 181)	

BMI: Body mass index
[a]DIPJ: Prognostic factor (limited evidence), [b]DIPJ: Not a prognostic factor (limited evidence), [c]DIPJ: Mixed evidence, [d]PIPJ: Prognostic factor (limited evidence), [e]PIPJ: Not a prognostic factor (limited evidence), [f]PIPJ: Mixed evidence

2.2.4 Discussion

2.2.4.1 Summary

Overall, 18 studies were identified from the systematic review assessing risk factors for the presence of IPJ osteoarthritis (128, 134-140, 164-173), whilst eight studies were identified from the systematic review assessing prognostic factors for the progression of IPJ osteoarthritis (170, 176-182). Heterogenous classification criteria were used across both studies. Older age in women (134, 137, 138, 168) and female sex (135, 136, 168, 172) were the only risk factors identified with moderate evidence for the incidence of radiographic IPJ osteoarthritis. For all other risk or prognostic factors, across both studies, none were found to have moderate evidence for radiographic, radiographic symptomatic, symptomatic, or clinical IPJ osteoarthritis incidence or progression.

It might be expected that older age and female sex were found to be risk factors for the presence of radiographic IPJ osteoarthritis. In the general population, incident hand osteoarthritis, measured through International Classification of Disease (ICD)-10 codes and the number of patients seeking medical treatment, is known to be most prevalent in middle-aged women, particularly around the age of menopause (26, 185). Capturing incident hand osteoarthritis in this way is likely to capture both symptomatic and radiographic disease, and disease at both or either of the IPJs and first CMCJs. In the systematic review, no studies investigated female sex and older age as possible risk factors for symptomatic IPJ osteoarthritis, and future studies should focus on the role of these potential risk factors.

Similarly, osteoarthritis experts consider female gender and age over 40 years as prognostic factors for the progression of hand osteoarthritis (76). However, in the systematic review assessing prognostic factors for the progression of radiographic IPJ osteoarthritis, female gender was found to have limited evidence for not being a risk factor, and older age was found to have inconsistent results. These results were influenced by the high risk of bias in these studies, and therefore to better understand the role of female sex and older age as potential prognostic factors for radiographic IPJ osteoarthritis progression, more robust studies are required, particularly with up to date statistical analysis.

To account for sex or gender being a risk factor, some studies were stratified by sex or gender. For example, dental occupation was assessed as a risk factor for the presence of radiographic IPJ osteoarthritis in men separately to women (164). In men, dental occupation was found to be a risk factor, whilst in women, dental occupation was not found to be a risk factor (164). Though the association was reported to be different across the genders, it is possible that other risk factors which have not been accounted for in the analysis play a role. In particular, within dentists, male dentists are known to work a higher number of hours compared to female dentists (186). This might lead to repetitive loading across the IPJs, resulting in microtrauma, which itself might be a risk factor for the presence of IPJ osteoarthritis. However, to better assess the role of multiple risk factors, studies assessing multiple risk factors together, such as phase 3 studies and prediction models, are required.

In both systematic reviews, IPJ osteoarthritis was diagnosed radiographically. When comparing risk factors for the presence of radiographic IPJ osteoarthritis with prognostic factors for the progression of radiographic IPJ osteoarthritis, there is conflicting evidence. Across both systematic reviews, female sex, older age, and diabetes were assessed. The results found that older age in women, older age in men, and female sex are all risk factors for the presence of IPJ osteoarthritis (134-138, 168, 172), whilst, when assessing prognostic factors, there was inconsistent evidence for older age in women and older age in men, and there was limited evidence for female sex not being a prognostic factor (176-178, 181). In comparison, diabetes was not found to be a risk factor for the presence of disease (136) but was found to be a prognostic factor for disease progression (180).

These results suggests that risk factors for the presence of radiographic IPJ osteoarthritis could be different to prognostic factors for the progression of the disease. For example, for diabetes, the results suggests that diabetes itself is not a strong enough risk factor to cause osteoarthritis, but if there are already osteoarthritic changes at the joint, diabetes contributes to further joint degeneration. Diabetes and hyperglycaemia are thought to be prognostic factors due to the induction of reactive oxygen species and cytokine production, leading to joint inflammation and the production of proteolytic enzymes (187). IPJs with osteoarthritis are likely to have some surrounding inflammation at the joint, which itself might be worsened by a hyperglycaemic state, leading to further disease progression. However, comparison of results across the systematic reviews is limited by differences across studies. For example, when comparing diabetes, the study assessing its role as a risk factor for the presence of radiographic IPJ osteoarthritis was cross-sectional in design, did not specify the proportion of males and females in the study, or the mean age, and classified osteoarthritis using the Altman (OARSI) atlas, whilst the study assessing its role as a prognostic factor was a prospective cohort study, included 60% females, with a mean age of 60.5 years, and classified osteoarthritis using the KL atlas (180) (136).

2.2.4.2 Potential limitations

Limitations with study population

Though the majority of studies included in the systematic reviews were population-based studies, some of these studies recruited participants from specific populations or groups of people. In particular, one study was taken from a registry (164), one study recruited patients from hospital (179), and in four studies, participants were selected based on pre-existing musculoskeletal or osteoarthritis conditions (128, 135, 167, 169, 180). These studies could therefore include specific groups of patients with pre-existing conditions or whom might have health seeking behaviours, leading to a selection bias, and the recruitment of participants with a higher proportion of IPJ osteoarthritis, in comparison to the general population. As such, this might over-represent the burden of osteoarthritis in these studies, resulting in the identification of risk factors which might otherwise not been seen in the general population. Instead, populated-based studies could be used as they are designed to be representative of entire populations, through which incidence and prevalence of disease can be estimated, with limited bias from confounders (188).

The incidence of hand osteoarthritis is higher in women than in men across all age ranges, and is known to peak in the 60 to 70 age range (26). However, in the systematic review for the presence of IPJ osteoarthritis, 13 studies included both men and women (128, 134-136, 139, 164, 165, 168-173). In the systematic review for the progression of IPJ osteoarthritis, three studies assessed only men (176-178), whilst five studies assessed both men and women (170, 179-182). Assessing IPJ osteoarthritis in men, in whom the incidence and prevalence of disease is known to be less than in women, is likely to lead to reduced power. In particular, assessing IPJ osteoarthritis in young men, such as those below the age of 60 years, is likely to result in fewer participants with osteoarthritis, biasing the associations between risk or prognostic factors with osteoarthritis towards the null.

The peak incidence of hand osteoarthritis occurs in a younger population, ages 60 to 64 years (remaining high until age 75 years), compared to the peak incidence of osteoarthritis at the hip and knee (from 70 years' old) (26). The age of participants was not reported by all studies in the systematic review assessing the presence of osteoarthritis. However, across the studies which did report age as an eligibility criterion, eight studies allowed a much younger age of participants for study inclusion (128, 135, 140, 165, 167, 168, 171, 173). Two of these eight studies were prospective cohort studies with follow-up periods of 15 to 17 years (135) and 24 years (165), and therefore some participants would still not be above the age of 60 years at the time of assessing the presence of IPJ osteoarthritis. The other six studies were either case control or cross-sectional studies, again with participants under the age of 60 years (128, 140, 167, 168, 171, 173). It is possible that the young age of participants might decrease the incidence osteoarthritis in the studies included in this systematic review, and therefore bias towards not detecting possible risk factors.

To more accurately capture the presence of IPJ osteoarthritis and its risk factors, studies should recruit participants whose age is between 60 to 75 years, at the time of osteoarthritis assessment.

Limitations with outcome definitions

Osteoarthritis is a chronic and progressive condition. Though the rate of IPJ osteoarthritis progression has not been studied, radiographic progression in 19% to 23% of patients has been identified in just a two year period (96). In a ten year period, spread into other hand joints not already affected by osteoarthritis at baseline, in participants who had at least one joint affected at baseline was between 79% to 88%, whilst worsening at a hand joint already affected by osteoarthritis at baseline was 61 to 72% (183). In the studies assessing the progression of IPJ osteoarthritis, the mean time of follow up ranged from 2.28 years (178), to 23.5 years (176). Studies with longer periods of followup would be more likely to diagnose osteoarthritis progression, as it is more likely to occur. Studies with shorter follow up periods might not have captured osteoarthritis progression over such a short time frame, particularly in patients whom might have a disease phenotype which progresses more slowly. If different phenotypes of the disease do exist, specifically phenotypes which progress more slowly compared to phenotypes which progress more quickly, such as erosive osteoarthritis, studies with shorter follow up periods are unlikely to detect phenotypes which progress more slowly. Further, if different prognostic factors exist for slower compared to faster progressing phenotypes, it is unlikely they would be identified in these studies.

Across both systematic reviews, all studies diagnosed IPJ osteoarthritis radiographically, using either the KL or Altman (OARSI) atlases. However, there are known to be some inconsistencies between the written descriptions and versions of the KL atlas, which has been updated by Kellgren and Lawrence (82). A systematic review of radiographic scoring methods for hand osteoarthritis assessed ICC, a measure of inter- and intra-reader reliabilities, for using all versions of the KL atlas to read hand radiographs (77). They reported the ICC for inter-reader reliabilities for the incidence of hand osteoarthritis was 0.84 to 0.96, and for the progression of hand osteoarthritis it was 0.83 (77). This suggests there is some difference between the way different readers might interpret hand radiographs using the KL atlas. It is possible that in some studies readers might have erroneously over-reported IPJ osteoarthritis, whilst in other studies different readers might have mistakenly under-reported IPJ osteoarthritis. Any under reporting IPJ osteoarthritis would result in decreased effect measured between the risk or prognostic factors and osteoarthritis, biasing results towards the null.

Across both systematic reviews, five studies used sum scores (for example, the sum KL score across IPJs for the presence of OA (168, 169), the sum osteophytes and joint space narrowing score as defined by the Altman atlas for the presence of OA (167), and an increase in KL sum score for OA progression (179, 180, 182)). Sum scores can be useful when diagnosing IPJ osteoarthritis progression, which can either be due to spread of osteoarthritis to multiple joints, or worsening of osteoarthritis at a joint already affected, as such scores assess multiple IPJs. However, for the presence of osteoarthritis, sum scores might include non-significant increase in score, such as from KL grade 0 to 1, both of which are considered to not be diagnostic of osteoarthritis. Instead, binary outcomes for the presence of osteoarthritis (such as the commonly used threshold of KL ≥2 to diagnose osteoarthritis) are likely to be more accurate and reproducible. During data extraction, it also became apparent that criteria used across studies to diagnose either IPJ osteoarthritis incidence or progression have not yet been developed. This lead to heterogeneity across studies in the way osteoarthritis was described, and prevented a meta-analysis. Further work is needed to develop a consensus definition for both incident (and the presence of) and the progression of hand osteoarthritis. I plan to undertake this work by chairing a new Hand Osteoarthritis Discussion Group at the OARSI World Congress 2021.

The association between radiographic and symptomatic hand osteoarthritis is poorly characterised. The systematic review for the presence of osteoarthritis identified studies which diagnosed IPJ osteoarthritis both radiographically and symptomatically. All 14 potential risk factors which were assessed for their association with clinical osteoarthritis were also assessed for their association with radiographic osteoarthritis. History of finger fracture and parity (yes versus no) were both found to be risk factors for radiographic osteoarthritis, but not for symptomatic osteoarthritis (167). However, for all other 12 potential risk factors, no association was found for either radiographic or symptomatic IPJ osteoarthritis. This might suggest that the risk factors for radiographic and symptomatic IPJ osteoarthritis are in fact similar, and that if a variable is not a risk factor for symptomatic IPJ osteoarthritis it is also unlikely to be a risk factor for radiographic IPJ osteoarthritis.

2.2.4.3 Strengths

These were the first systematic reviews to assess risk and prognostic factors for IPJ osteoarthritis. Studies included in the systematic reviews sufficiently separated IPJ from first CMCJ osteoarthritis, allowing for joint specific analyses. The QUIPS risk of bias tool was updated to more accurately reflect prognostic factor studies. The majority of studies in the systematic review of risk factors for the presence of osteoarthritis were either moderate or low risk of bias. Though almost all of the studies in the systematic review of prognostic factors for the progression of osteoarthritis were of high risk of bias, all of the studies used a prospective design, which is recognised as the most robust study design for prognostic factor studies due to the prospective time delay between the risk factor and the outcome (142).

2.2.4.4 Translating research to clinical practise

The results from these systematic reviews suggest that females with older age, and possibly those with a family history of Heberden's nodes are most likely to be at highest risk of the presence of radiographic IPJ osteoarthritis. These results suggest that clinicians might expect to see the presence of radiographic IPJ osteoarthritis in older females. However, as both of these risk factors are non-modifiable, it would be difficult to prevent the onset of the disease in this population.

Patient presenting to clinical settings often do so due to the onset of symptoms, such as pain, swelling, and loss of function. The systematic review was unable to find any risk factors for the presence of symptomatic IPJ osteoarthritis, suggesting it is still unclear what puts patients at highest risk of the presence of symptomatic IPJ osteoarthritis. Therefore, it is still difficult for clinicians to identify people at highest risk, or modify any potential risk factors.

Similarly, in patients who already have radiographic IPJ osteoarthritis, the systematic review was unable to find any prognostic factors for its progression. There was mixed evidence for male and female sex, suggesting that both male and female patients are likely to have disease progression. In these patients, it is currently still difficult to identify those at highest risk of radiographic IPJ osteoarthritis progression, and further research to identify and understand other prognostic factors which might also have an effect, such as age, are required. Additionally, further research is also required to understand whether prognostic factors for the progression of radiographic IPJ osteoarthritis are similar to those for symptomatic IPJ osteoarthritis progression.

2.2.4.5 Future research

These systematic reviews are the first to assess risk and prognostic factors for IPJ osteoarthritis. The identification of risk factors for IPJ osteoarthritis could be improved by studying middle-aged women, in whom hand osteoarthritis is known to have both the highest incidence and prevalence (26). All of the studies assessed radiographic IPJ osteoarthritis, and symptomatic osteoarthritis, often presenting to healthcare, was underrepresented and should be captured in future work. Therefore, the second part of this chapter aims to address these concerns by assessing potential risk factors in middle-aged women who present to hospital clinics.

Through describing the classification criteria for IPJ osteoarthritis, it has become clear that it is appropriate to classify the presence (and possible the incidence) of osteoarthritis as a binary outcome (yes/no). The progression of osteoarthritis should be assessed using an ordinal outcome, for either spread to additional joints, or worsening at a joint with osteoarthritis at baseline. Therefore, further chapters in this thesis will rely on such criteria.

There is also a paucity of phase 3 prognostic factor studies in the literature. Patients with IPJ osteoarthritis are likely to have multiple potential risk factors concurrently present. The next chapters of this thesis aim to increase understanding of multiple prognostic pathways due to the presence of multiple potential risk factors, and to better characterise the overall effect on the risk of IPJ osteoarthritis incidence and progression.

2.3 Study 2: Delphi Studies

2.3.1 Introduction

To develop Phase 3 studies, such as prediction and prognostic models built using data which is already collected, there needs to be a way to select potential candidate predictors for the models. One such way would be to assess the existing literature. From the systematic reviews above, it is clear that evidence surrounding risk factors for the presence of IPJ osteoarthritis, and prognostic factors for the progression of IPJ osteoarthritis are lacking. For the few risk factors which have been identified, evidence is affected by risk of bias, and the small number of studies. In this case, it is common to find there is a large number of potential risk factors collected in databases, which could be put into models, but for which there is not enough existing literature. In situations where evidence is sparce, and where the evidence which does exist is conflicting, consensus methods have been recommended to supplement existing knowledge (189). The results can then be used to inform Phase 3 studies.

Consensus methods are procedures executed over multiple rounds, over which individuals anonymously provide their opinion on a topic of interest (189-191). Summary measures of responses from the entire group are then analysed, with results presented to the individuals. Consensus methods include Delphi studies, expert panels (also known as nominal group studies), and consensus development conferences (189-193). Both Delphi studies and expert panels are also considered to be measurement instruments. Delphi studies are used to develop new ideas and to measure consensus. Consensus involves both the agreement or disagreement of each Delphi panel member around such ideas, and the agreement or disagreement between panel members (189, 192). Nominal groups can be used to both measure consensus, and then develop consensus in specific meetings (192, 193). Consensus development conferences are multi-disciplinary groups which engage in public meetings to hear evidence from experts and engage in questions from the general public, before developing consensus statements (193).

2.3.1.1 Objectives

The objectives were to perform Delphi studies to gain and measure consensus in identifying a) important risk factors for incident IPJ osteoarthritis, and b) important prognostic factors for the progression of IPJ osteoarthritis, which hand surgeons most commonly identify in their clinical practice.

2.3.2 Methodology

Both Delphi studies used the same methodology as described below. However, Delphi panel members were unique to each Delphi study.

2.3.2.1 Ethical approval

Ethical approval was not required, after consultation with the Joint Research Office, Oxford University Hospitals NHS Foundation Trust, as these studies were considered to be a form of peer review.

2.3.2.2 Study design

Each Delphi study was developed by first recruiting a Delphi panel, a group of clinicians with active experience relating to hand osteoarthritis (regarded as experts in this field) (192). The use of a panel prevents the effect of a dominant individual or group of dominant individuals exerting any bias when attempting to reach consensus (known as 'process loss') (192). There was no a priori target sample size for the number of panel members for each Delphi study.

When running a Delphi study, panel members are often presented with a list of possible variables, which they must assess and, through consensus, select an important subgroup from. Possible variables can be taken from an existing dataset, so that results from the Delphi study can be used to inform secondary analyses of the existing dataset.

There are no rules on how to assess consensus between Delphi panel members. Following the first time (first round) the panel members assess the variables, feedback on the consensus exercise is provided. This allows the panel members to re-consider their initial response (194). Delphi studies can either continue for a pre-specified number of rounds, or until an a priori consensus threshold has been met (known as a 'classic Delphi') (191).

2.3.2.3 Recruitment of Delphi panel members

Experts for the Delphi panels were recruited from the BSSH registry of full members. In February 2019, there were 420 full members (consultant hand surgeons in the UK) (195). Panel were recruited through an email invitation to express interest, between 17th to 31st January 2019 (two weeks). Respondents were randomly allocated to either the Delphi study for incident IPJ osteoarthritis, or the Delphi study for the progression of IPJ osteoarthritis.

2.3.2.4 Selection of risk factors

Within hand osteoarthritis, it is known that the disease most commonly affects women (26, 185). Therefore, to better identify important risk and prognostic factors for IPJ osteoarthritis, a list of potential risk and prognostic factors were taken from the baseline year (year of recruitment) of the Chingford Study.

The Chingford Study is a population based prospective cohort study, designed to study risk factors for osteoarthritis and osteoporosis. At baseline, only women between the ages of 45 to 64 years were recruited, and 694 different clinical and anthropometric variables collected. In order to present a more reader-friendly list of possible risk and prognostic factors to the Delphi panel, the 694 variables were used to form 85 composite risk and prognostic factors (the 85 composite risk and prognostic factors are shown in Appendix 2.1). These composite risk and prognostic factors were developed by grouping similar variables, and also by creating new composite variables from co-linear variables (for example, weight and height were used to make a composite variable for BMI).

In order to capture any other potential risk or prognostic factors which had not been collected in the Chingford Study, in the first round of the Delphi studies, panel members were asked to suggest any other important risk/ prognostic factors which had not been listed. These were then included in the second round of the Delphi, for panellists to assess.

2.3.2.5 Statistical analysis

All analyses were performed in Microsoft Excel version 16.49.

Panellists were initially presented with the 85 composite risk or prognostic factors from the Chingford Study, in a 'first' Delphi round (questionnaire from round 1 of the Delphi study assessing risk factors for incident IPJ osteoarthritis is shown in Appendix 2.1. The same variables were used as prognostic factors for round 1 of the Delphi study assessing prognostic factors for the progression of IPJ osteoarthritis). As each variable in the Chingford Study was captured as it was considered to be a potential risk factor for osteoarthritis, panellists were asked to rate the importance of each potential risk or prognostic factor, using a Likert scale graded from one ('no importance) to five ('extreme importance') based on risk factors they have recognised in the patients they manage in their hand surgery clinics.

The list of risk or prognostic factors and the Likert scale were provided as an electronic questionnaire on Research Electronic Data Capture (REDCap) software (196). An individual link to each REDCap questionnaire was emailed to panellists, with a 14-day response policy. Results were then exported to Microsoft Excel and analysed. The anonymised results were presented to panellists after each round.

A ‘classic Delphi approach’ was used, whereby results were analysed immediately after the 14-day response policy, and the original study design was maintained as the Delphi studies progressed. The results were analysed using a priori consensus criteria (Figure 2.2). Each risk or prognostic factor was assessed for consensus across the Delphi panel members. For each risk or prognostic factor, there could either be consensus identifying it as an important risk or prognostic factor in patients in hand surgery clinics (‘inclusion consensus’), consensus identifying it as not an important risk or prognostic factor in patients in hand surgery clinics (‘exclusion consensus’), or no consensus (197). Risk or prognostic factors which reached either ‘inclusion consensus’ or ‘exclusion consensus’ were removed from the REDCap questionnaire. Risk or prognostic factors which did not reach consensus were kept in the REDCap questionnaire, and re-presented to the panel members in a subsequent Delphi round.

In the second and subsequent Delphi rounds, panellists were again asked to complete the REDCap questionnaire rating the importance of the risk or prognostic factors which did not meet consensus in the previous round. There results were assessed using a priori consensus criteria for ‘inclusion consensus’, ‘exclusion consensus’, ‘inter-round stability of non-consensus’ (i.e.- lack of consensus over two consecutive rounds) and no consensus (Figure 2.2) (198). Risk or prognostic factors found to have ‘inter-round stability of non-consensus’ were then grouped with risk or prognostic factors found to meet ‘exclusion consensus’. Risk or prognostic factors which did not meet consensus were again presented to the Delphi panels through a REDCap questionnaire in an additional Delphi round. This was repeated until all risk or prognostic factors had either ‘inclusion consensus’ or ‘exclusion consensus’.

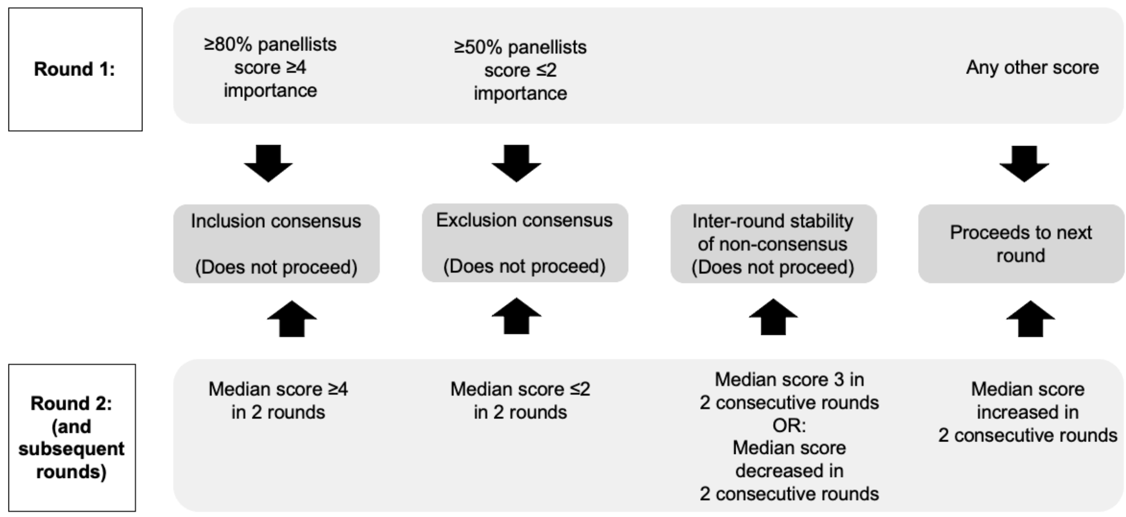

Figure 2.2: Criteria for consensus and non-consensus in the Delphi studies

2.3.3 Results

Eighteen hand surgeons volunteered to form the Delphi panels. There were 11 (61%) orthopaedic consultants and seven (39%) plastic surgeon consultants. Four (22%) of the panel members were female. Panel members worked at a variety of geographical areas, with not more than two panel members identified as working in the same region. Nine surgeons were randomly allocated to each Delphi study.

2.3.3.1 Important of risk factors for incident IPJ osteoarthritis

Delphi panel members

Due to non-response of panellists between Delphi rounds, there was attrition of panel members. Seven panellists completed the first Delphi round questionnaire, six completed the second Delphi round questionnaire, and four completed the final Delphi round questionnaire.

Importance of risk factors

No risk factors met ‘Inclusion consensus’ in the first Delphi round (Figure 2.3). A new risk factor was also introduced by the Delphi panel in the first round (‘direct injury’). In the second Delphi round, two risk factors met ‘Inclusion consensus’ (‘older age’, ‘family history of hand osteoarthritis in mother’), and in the third Delphi round, one risk factor met ‘Inclusion consensus’ (‘direct injury’) (Figure 2.3). Only three Delphi rounds were required.

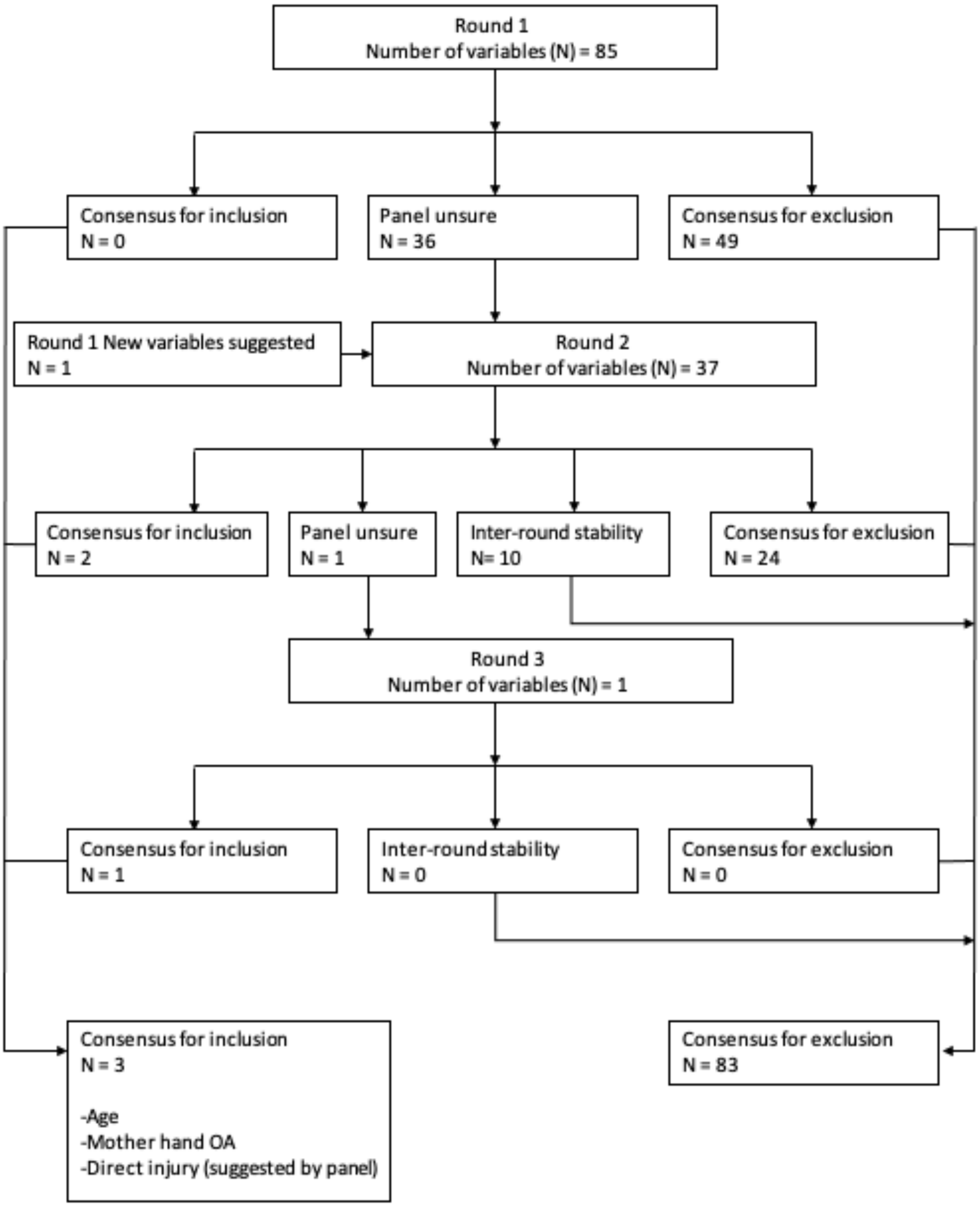

Figure 2.3: Flow chart of important risk factors in the Delphi study for incident IPJ osteoarthritis

OA: Osteoarthritis

2.3.3.2 Important risk factors for the progression of IPJ osteoarthritis

Delphi panel members

Due to non-response of panellists between Delphi rounds, there was attrition of panel members. Six panellists completed the first Delphi round, and five completed the second, third, and final Delphi rounds.

Importance of prognostic factors

One risk factor met 'Inclusion consensus' in the first Delphi round ('older age') (Figure 2.4). Three new prognostic factors were also introduced by the Delphi panel in the first round ('previous ligamentous injury to IPJs', 'previous finger fractures', 'previous radiation to hands'). In the second Delphi round, two prognostic factors met 'Inclusion consensus' ('family history of hand osteoarthritis in mother' and 'family history of hand osteoarthritis in brother'), in the third Delphi round, one prognostic factor met 'Inclusion consensus' ('family history of hand osteoarthritis in father'), and in the fourth round no prognostic factors met 'Inclusion consensus' (Figure 2.4). Four Delphi rounds were required.

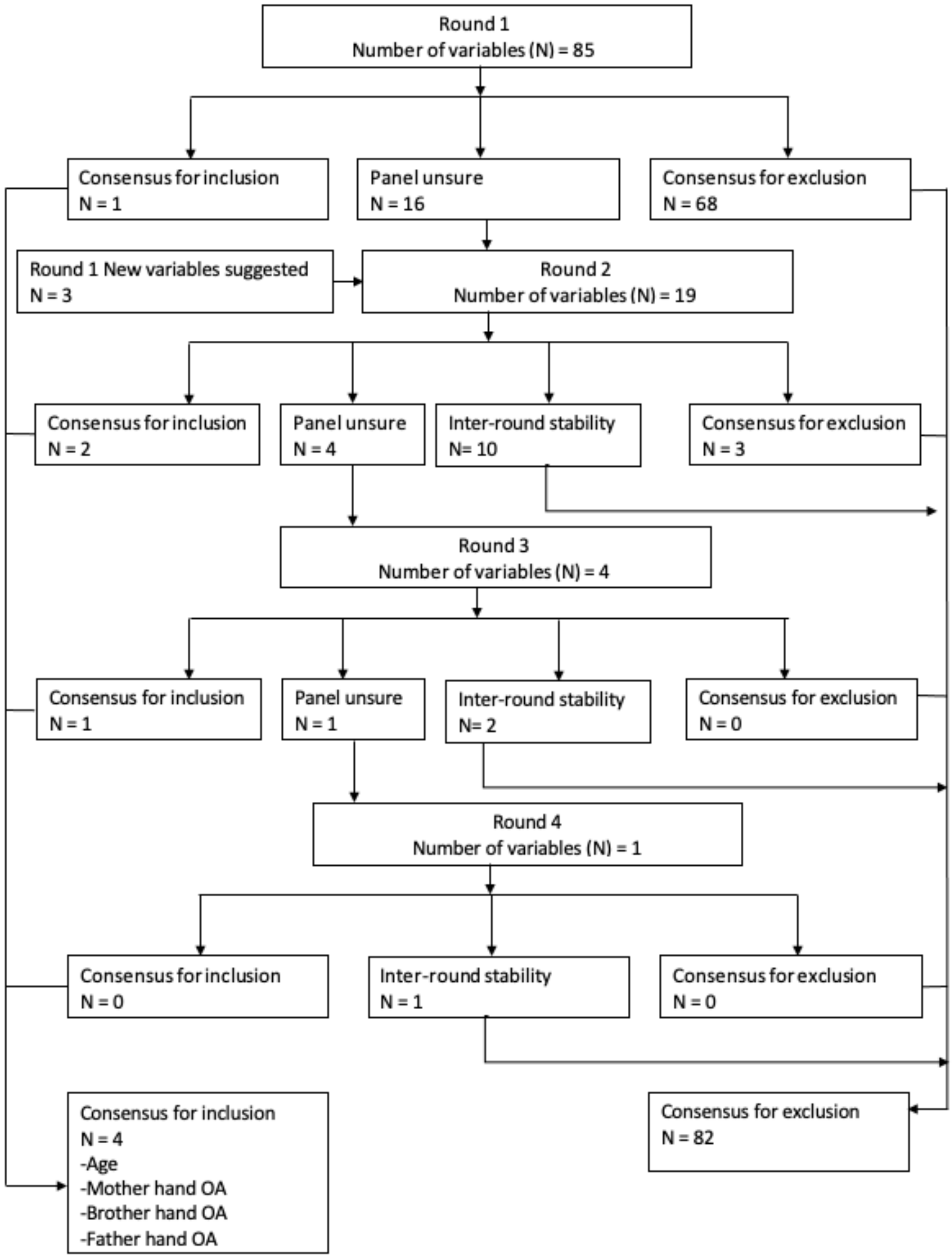

Figure 2.4: Flow chart of important prognostic factors in the Delphi study for the progression of IPJ osteoarthritis

OA: Osteoarthritis

2.3.4 Discussion

2.3.4.1 Summary

The Delphi studies concluded after a few rounds, despite using the 'classic' approach. This suggests that the panellists were able to reach consensus, and agree on which variables were or were not important risk/ prognostic factors, in a fast and productive manner. This indicates that the risk/ prognostic factors which were identified as being important are likely to be widely recognised by hand surgeons, and there is agreement within this specialist community. The risk/ prognostic factors were also similar between the two Delphi studies (older age and family history), indicating that surgeons may not see differences between patients who develop IPJ osteoarthritis and in those in whom it progresses.

When comparing the results of the Delphi studies to the systematic reviews, the three risk factors identified by the Delphi study investigating the importance of risk factors for the incident IPJ corresponded with the potential risk factors found in the systematic review. The systematic review also identified parity as a potential risk factor. This variable was available to the Delphi panel through the Chingford Study, but was not identified by the Delphi panel as being important. The Chingford Study does not include male participants, so potential risk factors relating to men identified by the systematic review were not included in the Delphi study. The Delphi panel did not rate any potential risk factors as important for those variables which were identified as not being risk factors in the systematic review. These results suggest that potential risk factors observed in clinical practice do correspond with what is identified in the literature.

The Delphi studies assessed the importance of potential risk factors, whilst the systematic reviews investigated whether risk factors exist, and if so, which these are. Therefore, even though a comparison of results between the two studies is possible, not all of the variables in the systematic reviews correspond to those available in the Chingford Study, and vice versa.

The Delphi study assessing important risk factors for the progression of IPJ osteoarthritis identified age as an important prognostic factor, whilst this was found to have conflicting evidence in the corresponding systematic review. The Delphi panel also identified family history, though this was not investigated in any studies included in the systematic review. The systematic review identified diabetes as potential risk factor. Though diabetes was not a variable in the Chingford Study, use of diabetic medication and fasting glucose were. The Delphi panel did not find that either of these were important risk factors. These results might be due to the small number of studies included in the systematic review. It is possible that the results from the Delphi panel represent a sub-group of patients whose condition is severe enough to warrant referral to tertiary care. The systematic review only assessed risk factors for radiographic IPJ osteoarthritis, whilst patients with symptomatic disease might also be at higher chance of being under the care of hand surgeons.

2.3.4.2 Potential limitations

<u>Limitations with study population</u>

From 450 hand surgeons who could have taken part in the Delphi study, only 18 volunteered. Clinicians who self-select to be part of Delphi panels or nominal groups have been shown to be representative of their colleagues (193). Though the percentage of panel members is small, they are representative of the orthopaedic to plastic surgeon ratio of members reported in a 2006 BSSH audit showing a 2:1 ratio, respectively (199). The BSSH has not published data on the male:female ratio of members, though, throughout all surgical specialities, 12% of consultants are female (200). When including higher trainees and specialists doctors, 29% of plastic surgeons are female, whilst this is 11% in orthopaedic surgeons (200). With a 22% prevalence of female consultants on the Delphi panels, it is possible that females are slightly over-represented. There was also a high attrition rate of panel members, and the reason for this is unclear. It is possible that panel members who remained throughout the Delphi studies might represent surgeons who are more interested in academia, have more experience in managing hand osteoarthritis, or have particular views they wanted to share.

Panel members were asked to assess the important of risk or prognostic factors based on their clinical experience. It is almost certain that patients who are in hand surgery clinics have already sought healthcare from their GP. The lack of improvement of such treatment might reflect the severity of their disease, and prompt the referral to a hand surgery clinic. Therefore, patients in hand surgery clinics might have more severe disease at presentation to clinic. Health-seeking behaviour in patients with hip or knee osteoarthritis is known to be higher in patients who have had previous care from health providers (201). Therefore, it is possible that these patients may also over-present compared to the general population, if they have other medical conditions.

Limitations with data variables

The study assumes that all variables presented to panellists are risk or prognostic factors for IPJ osteoarthritis. This is because they were taken from the Chingford Study, where they were captured as they are considered likely to be risk or prognostic factors for either or both of osteoarthritis and osteoporosis. However, it is possible that some of the variables captured in the Chingford Study have not yet been studied for their association with IPJ osteoarthritis. To better discern whether the variables presented to the panellists are indeed risk or prognostic factors for IPJ osteoarthritis, their association should be further investigated. This could be most appropriately performed through phase 3 studies, in which prediction or prognostic models can be used to determine the risk of the outcome based on multiple risk or prognostic factors being present or absent. This will be performed in the following chapters of this thesis.

Limitations with statistical analysis

It is possible panellists could suggest that some variables are not actually risk or prognostic factors for IPJ osteoarthritis, as the Likert scale ranged from one ('no importance') at the lowest end of the scale. If a risk or prognostic factor was found to have a consensus of one out of five, it is possible that the panellists either recognised it as a risk or prognostic factor but considered to be of no importance in clinical practice, or they did not consider it to be a risk of prognostic factor in the first place.

2.3.4.1 Strengths

This is the first study to assess how hand surgeons view potential risk/ prognostic factors for IPJ OA. The assessment of patients in clinics is likely to represent more symptomatic disease, such as pain and loss of function, which could fill the paucity of information found in the systematic reviews. Panel members were able to suggest potential risk factors, which allowed for the assessment of variables not included in the Chingford Study. High cut off thresholds for 'inclusion consensus' ensured confidence in the panel's decision, and similarly strict thresholds for 'exclusion consensus' allowed many variables within this realm to be re-assessed between rounds. The use of a classic Delphi (191) approach allowed for the self-regulation of the Delphi rounds, which should capture all possible results.

2.3.4.2 Translating research to clinical practise

The clinical implications of these Delphi studies are limited, as there were a small number of panellists across both Delphi studies, and high attrition rates across Delphi rounds. It is also unclear whether the hand surgeons were considering clinical, symptomatic, radiographic, or radiographic symptomatic disease during these studies, and all studies assessed potential risk or prognostic factors in women only (as variables were taken from the Chingford Study). In this context, the results suggest that hand surgeons think that older age and a family history are the most important risk and prognostic factors for IPJ osteoarthritis, and that direct injury to the joint is also an important risk factor for IPJ osteoarthritis, in women.

Patients who present to hand surgery clinics (i.e.- tertiary care) are most often those who have been referred from primary care, commonly due to failure of conservative management, and often requiring invasive treatment, such as steroid injections or joint surgery. The results from the Delphi studies suggests that older female patients with relevant family histories are most likely to require these types of invasive management techniques.

2.3.4.3 Future research

Hand injury was suggested by panel members in both Delphi studies. However, only the Delphi study for incident IPJ osteoarthritis reached 'inclusion consensus' and agreed that hand injury is an important risk factor. Given the interest in the role of hand injury as a risk factors for incident osteoarthritis, further chapters in this thesis will characterise the burden of hand injury and assesses its relationship with incident IPJ osteoarthritis.

3 CHAPTER 3: PREDICTION MODEL: INCIDENT RADIOGRAPHIC IPJ OSTEOARTHRITIS

3.1 Chapter Aims

In this chapter, I will develop a prediction model for incident radiographic IPJ osteoarthritis, based on multiple potential predictors, including those identified from the systematic review and Delphi study (chapter 2). In this chapter, IPJ osteoarthritis always refers to the radiographic classification.

3.2 Introduction

The systematic review identified some potential risk factors for incident IPJ osteoarthritis (chapter 2) (148). Most predictors were assessed in isolation to other predictors, though, in clinical practice, people are more likely to have a combination of multiple risk factors present, all affecting the overall risk of the disease. When multiple risk factors or predictors for a disease are present, it is possible to use a multivariable analysis to first determine the importance of these risk factors, and then to estimate the risk of disease in the presence of a combination of risk factors (142). Initially, this is done through Phase 1 studies, in which exploratory analyses are performed to identify associations between individual possible risk factors and the outcome (143, 144). Once these associations have been identified, Phase 2 studies are used to test and confirm the associations (143, 144). Finally, Phase 3 studies are used to understand the prognostic pathways, and the complex relationships between multiple variables (143, 144).

Phase 3 studies can be used to inform clinical decision tools which are themselves used to estimate the likelihood of disease, using clinical information such as patient histories, clinical examinations, and laboratory results (202). An example of a commonly used clinical decision tool for orthopaedic-related conditions in emergency settings are the Ottawa ankle rules, to determine whether radiography is needed after ankle injury (203). However, clinical decision tools rely on clinicians correctly recalling a large number of rules (204). Instead, heuristics, more simplistic decision trees, are more commonly used in the everyday decision making and judgements by the human mind (205). In decision making using heuristics, sequential inference is used to eliminate differential diagnoses in a stepwise manner. An example of using heuristics clinically, is when identifying causative organisms of infection, to inform the appropriate use of antibiotics, and prevent treatment resistance (204). Using heuristics is particularly useful when working under restricted time, with limited information, and without the power of technology or computers (206, 207).

More recently, statistical tools to estimate risk and probabilities have been developed. When considering the incidence or development of disease, these tools are referred to as prediction models, with the variables referred to as risk factors, whilst when considering the progression of disease, these tools are referred to as prognostic models, with the variables termed prognostic factors (142). Prediction or prognostic models are particularly useful when determining an outcome for an individual person, based on their specific risk factors (or protective factors). Patients might or might not be unwell, and the future long-term risk or prognosis of a disease can be estimated. This is unlike the more broad definition of prognosis in the medical literature, which refers to the course of a disease in general, across the population (142). Prediction or prognostic models are not used to test causation (though all causal factors are always predictive or prognostic factors), but instead test association (142). A commonly used prediction tool is the Apgar score, a scoring system to determine the condition of a new-born baby using five risk factors: heart rate, respiratory effort, muscle tone, reflex irritability, and colour (208). Another well-known risk prediction tool is the Acute Physiology, Age, Chronic Health Evaluation (APACHE) III tool, used in critically ill patients (209). There are two results from the APACHE III tool, the first is a risk stratification for a patient into a defined risk group, and the second is from a predictive equation to estimate the risk of an individual patient's mortality (209).

To date, a prediction model has been developed to assess the risk of incident hand osteoarthritis in men (210). In this model, osteoarthritis was defined at 40 years' follow-up, using ICD-10 codes (210). These codes take into account 'arthrosis' of the 'wrist/hand/forearm', and do not separate IPJ and first CMCJ osteoarthritis. The codes also allow for osteoarthritis to be diagnosed through either clinical examination, such as Heberden's nodes and Bouchard's nodes in the IPJs, or through imaging such as radiographs. There is conflicting evidence for the relationship between radiographic and symptomatic hand osteoarthritis, and the prevalence of radiographic hand osteoarthritis is reported to be higher than that of symptomatic hand osteoarthritis (92, 93, 95, 96). This suggests that predictors for radiographic and symptomatic osteoarthritis might be different to each other, and indeed my systematic review found differences between potential predictors for the development of radiographic and symptomatic IPJ osteoarthritis (chapter 2). By using a wide outcome definition in their prediction model (210), multiple subtypes of osteoarthritis were likely to be captured. This may have contributed to the poor model performance, with the study reporting the area under the receiver operating characteristic curve (AUC) as 0.62 (95% confidence interval (CI) of 0.58 to 0.64), a sensitivity of 66% and a specificity of 47.8%. These results indicate the model is not able to accurately predict the risk of the hand osteoarthritis development. In this study, the prediction model was developed in middle-aged men, with 50% of the study participations developing osteoarthritis at follow-up (210). The incidence of osteoarthritis in the hands is known to be higher in women than in men, and peaks in the 60 to 70 year age range (26). Therefore, it is likely that this model was underpowered, which itself could lead to overfitting of the data. This model is also not generalisable to the population in which osteoarthritis in the hand joints is most prevalent. At a later date, the model was re-developed in women with a mean age of 50.9 years (211). The re-developed model reported an AUC of 0.62 (95% CI: 0.59 to 0.64), again reflecting poor model performance.

Separate prediction models for osteoarthritis development at the IPJs and at the first CMCJs should be developed, to account for each of these possibly representing different disease subtypes.

Prediction models for the development of osteoarthritis in hand joints should also be performed in a prospective cohort of middle-aged women, to reflect the incidence of the disease in the population it most commonly affects. This will also ensure a sufficiently high number of events in the study, to minimise overfitting of the data (26). Prospective cohort studies might also allow important potential predictors to be captured. For example, in my Delphi study, 'direct injury' was identified as an important risk factor for the development of IPJ osteoarthritis seen in clinical practice by hand surgeons (chapter 2). In my systematic review, only a history of finger fracture was assessed, even then in only one study, resulting in limited evidence for a history of finger fracture being a potential predictor for the development of IPJ osteoarthritis (chapter 2). If a prediction model is built using a prospective cohort study, and direct joint injury or fracture is captured, it can be included in the model as a candidate predictor, allowing for its importance in predicting the development of IPJ osteoarthritis to be more robustly assessed.

3.2.1 Objective

The objective was to develop a prediction model for incident radiographic IPJ osteoarthritis, in middle-aged women, using a prospective population-based cohort study.

3.3 Methodology

3.3.1 Reporting Guideline and Ethical approval

The reporting of this model followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guideline (212). There is ethical approval in place for ongoing analysis of The Chingford 1000 Women Study (South Central- Oxford A Research Ethics Committee (REC): REC reference 13/SC/0156), and this study did not require further approval.

3.3.2 Study design

There are three main stages in the methodology and use of prediction or prognostic models: model development, validation of the model, and assessment of the clinical impact of the model. The development of a model can be complicated, and there are a number of steps which should be followed, including defining the outcome, predictors, building the model, internally validating it, and then assessing its performance, before externally validating it and testing its clinical utility (detailed in Appendix 3.1).

3.3.3 Data sources

I identified multiple international prospective cohort studies analysing osteoarthritis, to determine which ones I could use to develop and externally validate the prediction model. Initially, I investigated the presence of hand radiographs in these studies. I was able to identify the Chingford Study, based in the UK, with hand radiographs at baseline and at 10 and 20 years' follow-up (213). I also identified The Johnston County Osteoarthritis Project (JoCo Project), based in North Carolina, with hand radiographs taken at three time intervals (a more detailed description is provided in section 4.3.3). I identified the Rotterdam Study (Rotterdam Elderly Study), which is composed of three cohorts, set up to study neurogeriatric, cardiovascular, locomotor and ophthalmic diseases (214). Hand radiographs have been taken at baseline and multiple follow-up periods. However, the Rotterdam Study is not accessible outside of the Erasmus University Medical Centre. The Framingham Heart Study, designed to study cardiovascular diseases, had hand radiographs taken at baseline and follow-up intervals, but it was unclear how these had been read, and a substantial fee was required for access (215). The Baltimore Longitudinal Study of Aging (216), the Twins UK data (217), the Tasmanian Older Adult Cohort Study (218), and the Cohort Hip and Cohort Knee (219) all include hand radiographs but only at one time point. No hand radiographs were available from the Study of Osteoporotic Fractures (220), Osteoarthritis Initiative (221), the Multicenter Osteoarthritis Study (222), or the Health, Aging and Body Composition Study (223).

Therefore, either the Chingford Study or the JoCo Project could be used to develop the prediction model. The Chingford Study was chosen to develop the prediction model in this chapter, as it includes only middle-aged women, a population in which the incidence of hand osteoarthritis is high (26). The JoCo Project includes both men and women, and has a smaller sample size of women compared to the Chingford Study. As data in the Chingford Study was so phenotypically rich, it was not possible to externally validate the prediction model, as no other cohort study captured similar variables (used as candidate predictors in the model) to the Chingford Study (see Table 4.3 in Chapter 4 for a comparison of similar candidate predictors between the Chingford Study and JoCo Project).

The Chingford 1000 Women Study

The Chingford Study was originally developed to investigate predictors for osteoarthritis and osteoporosis in multiple joints (213). The study began in 1992, using the age-sex register at a GP in Chingford, East London. There was a 78% response rate and 1,003 women aged between 45 and 64 years were recruited. Previous studies have shown that the women recruited were found to be representative of the general UK female population at that time (224, 225).

Six hundred and ninety-three participant characteristics were recorded using standard questionnaires and examination, and hand radiographs were taken during the recruitment year (known as Y01). Repeat hand radiographs were taken ten years later (known as Y11) and 19 years later (known as Y20). For this study, participant characteristics and hand radiographs taken at Y01 are referred to as ‘baseline’, and hand radiographs taken at Y11 are referred to as ‘follow-up’. The paired radiographs were read in known time order by two trained readers (TS and DH, with a KL grade reported after a consensus meeting) using the KL atlas, giving each IPJ one KL grade at baseline and one KL grade at follow-up (80). ICC (κ) of 0.7 to 1.0 have been reported (226). The KL atlas was chosen as it was identified as the most commonly used classification criteria in the systematic review (Chapter 2), and has been used across multiple hand osteoarthritis datasets, which would enable future external validation of the model. Additionally, unlike the KL atlas which uses a threshold of grade ≥2 as diagnostic of osteoarthritis, other radiographic classification criteria which score individual features often do not have similar pre-determined thresholds for the diagnosis of osteoarthritis, making it difficult to define study outcomes. I attempted to read hand radiographs at Y20, but this was not possible, due to severe rotation of the hands on the films, prohibiting visualisation of many of the joints.

3.3.4 Study participants

Participants without radiographs at baseline and follow-up, and participants with unreadable radiographs at baseline or follow-up (for example, all of the fingers were not captured) were excluded. Participants with osteoarthritis at baseline (KL ≥2 in ≥1 IPJ), and those with random error of radiographic reading (for example, a decrease in KL score at follow-up compared to baseline) were also excluded. Participants with radiographs at baseline which did not show radiographic osteoarthritis (KL <2 in all IPJs) were eligible for the current study (Figure 3.1).

3.3.5 Outcome

The systematic review (Chapter 2) showed that there are multiple definitions of incident IPJ osteoarthritis, and therefore, to include any incident IPJ osteoarthritis, the outcome definition was broad, defined as KL ≥2 in ≥1 IPJ at follow up (binary outcome: yes/ no). Time to event data was not recorded and therefore it was not possible to assess at which time point participants developed IPJ osteoarthritis. All participants were followed up for ten years. This means there is a fixed ten-year period between measurement of the candidate predictors and the diagnosis of incident IPJ osteoarthritis and a survival model (i.e.- a Cox regression model) could not be explored as there was no censoring.

From 1,003 participants in the Chingford Study, 304 (30.3%) participants did not have radiographs and 34 (3.4%) did not have readable radiographs (Figure 3.1). 665 participants had readable radiographs, of which 206 (31.0%) had IPJ osteoarthritis at baseline and were excluded. Therefore, 459 participants were included in the study, and of these 202 (44.0%) had developed IPJ osteoarthritis at follow up (Figure 3.1). A comparison of participants from the Chingford Study with incident IPJ osteoarthritis at follow-up, without incident IPJ osteoarthritis at follow-up, and without hand radiographs is presented below in section 3.4.1. No erosive IPJ osteoarthritis was identified in the Chingford Study.

Sensitivity analysis

To assess the performance of the model if the outcome definition was stricter, two sensitivity analyses were performed.

a) Incident osteoarthritis as ≥2 IPJs with KL ≥2 at follow-up

In the sensitivity analysis for ≥2 IPJs with incident osteoarthritis, participants with incident osteoarthritis in only one IPJ were excluded.

b) Incident osteoarthritis as ≥3 IPJs with KL ≥2 at follow-up

In the sensitivity analysis for ≥3 IPJs with incident osteoarthritis, participants with incident osteoarthritis in only one or two IPJs were excluded.

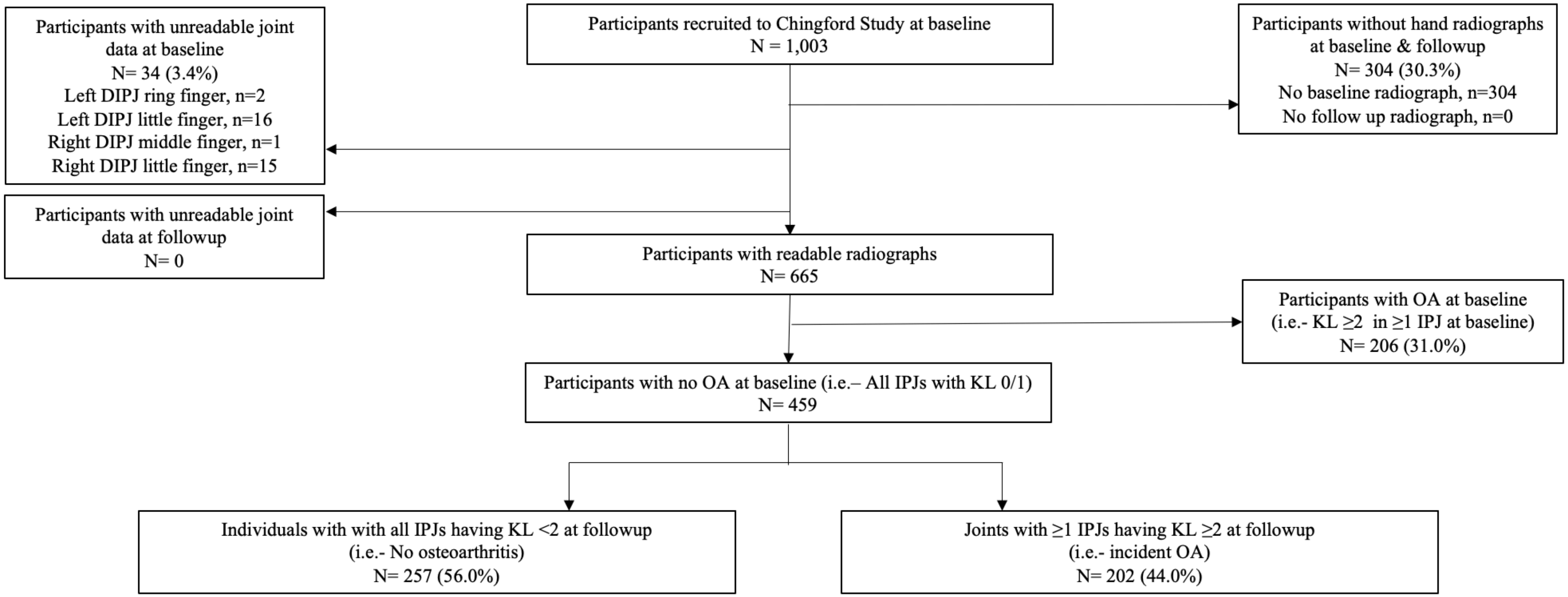

Figure 3.1: Flowchart of participants included from The Chingford 1000 Women Study

DIPJ: Distal interphalangeal joint; IPJ: Interphalangeal joint; KL: Kellgren Lawrence; OA: Osteoarthritis

3.3.6 Sample size

The sample size of the prediction model was fixed, as it was restricted to the number of individuals in the Chingford Study and it was not possible to recruit additional study participants. To minimise the risk of overfitting the model - producing a model which corresponds too closely to the dataset and incorrectly considers noise or residual variation as part of the data structure - the number of candidate predictors in the model was minimised. As such, the number of candidate predictors was selected using sample size criteria (227-229).

The sample size is the number of study participants required to fit the model. The sample size calculation takes into account the corresponding model fit ($R^2_{\text{Cox Snell}}$), the number of candidate predictors, and a recommended shrinkage factor of 0.9 (227-229). The sample size is (227-229):

$$\frac{number\ of\ candidate\ predictors}{(shrinkage - 1)\ln(1 - \frac{\text{R2Cox Snell}}{shrinkage})}$$

The $R^2_{\text{Cox Snell}}$ is taken from similar prediction models in the literature. However, in the absence of such studies, an *a priori* maximum $R^2_{\text{Nagelkerke}}$ can be determined, using the number of participants and the proportion of participants with the outcome in the study. The $R^2_{\text{Cox Snell}}$ can be between 15% of the maximum $R^2_{\text{Nagelkerke}}$, and up to 40% of the maximum $R^2_{\text{Nagelkerke}}$. The maximum $R^2_{\text{Nagelkerke}}$ is:

$$1 - (outcome\ proportion^{outcome\ proportion} * proportion\ without\ outcome^{proportion\ without\ outcome})^2$$

In the current study, with a fixed sample size of 459 participants and an outcome prevalence of 44% (202/459 with incident IPJ osteoarthritis), the corresponding maximum $R^2_{\text{Nagelkerke}}$ value is:

$$1 - (0.44^{0.44} * 0.56^{0.56})^2 = 0.74$$

Therefore, in the current study, if the $R^2_{\text{Cox Snell}}$ is 15% of the maximum $R^2_{\text{Nagelkerke}}$, it is:

$$0.15 * 0.74 = 0.11$$

And for the dataset (sample size of 459), the maximum number of candidate predictors is six.

$$\frac{6}{(0.9-1)\ln(1-\frac{0.11}{0.9})} = 451$$

Alternatively, in the current study, if the $R^2_{\text{Cox Snell}}$ is 40% of the maximum $R^2_{\text{Nagelkerke}}$, it is:

$$0.40 * 0.74 = 0.30$$

And for the dataset (sample size of 459), the maximum number of candidate predictors is 18.

$$\frac{18}{(0.9-1)\ln(1-\frac{0.30}{0.9})} = 446$$

To prevent overfitting, penalisation methods can then be used (described below in 3.3.8).

3.3.7 Candidate predictors

The sample size calculation found that between six to 18 candidate predictors could be included in the model.

Where multiple similar variables existed, a composite variable was created, for example weight and height were used to create BMI. Multiple similar variables were also tested for co-linearity using the Pearson's correlation coefficient (with a cut off of ≥0.6), and where variables were co-linear, the variable with the least amount of missing data was selected. Variables not related to the participant, such as those relating to their husband, were also excluded. Candidate predictors were chosen based on biological plausibility, and the results from both the systematic review and Delphi study (Chapter 2).

For this model, 18 candidate predictors were chosen as listed below. The methods of data capture for each candidate predictor, and how the data was manipulated for the current study, are described in Appendix 3.2.

1. Age
2. Occupation (manual versus non-manual)
3. BMI
4. Systolic blood pressure
5. History of hand fracture (yes versus no)
6. Age at menarche
7. Reached menopause (yes versus no)
8. History of live births (yes versus no)
9. History of miscarriage (yes versus no)
10. History of hysterectomy (yes versus no)
11. History of using the oral contraceptive pill (yes versus no)
12. History of using hormone replacement therapy (yes versus no)
13. History of smoking (ever versus never)
14. History of alcohol use (ever versus never)
15. History of knee osteoarthritis in family (yes versus no)
16. History of hand osteoarthritis in family (yes versus no)
17. History of radiographic knee osteoarthritis (yes versus no)
18. History of radiographic first CMCJ osteoarthritis (KL $\geq$2 (yes) versus KL <2 (no))

Outliers

Continuous candidate predictors were assessed for outliers. An outlier is defined as a value which is three times the interquartile range above the third quartile or below the first quartile (230). Box plots were used to visualise any outlier data for each continuous candidate predictor. Outliers were considered for biological plausibility, and if thought to be biologically implausible, were coded as missing data (231).

Four continuous candidate predictors were assessed for outliers: age, BMI, systolic blood pressure, age at menarche (Appendix 3.3). No outliers were identified for age; ten outliers were found for BMI, but all were considered to be biologically plausible; one outlier was found for age at menarche, and also thought to be biologically plausible; three outliers were found for systolic blood pressure, and all were thought to be clinically implausible findings in a community setting, and were therefore re-coded as missing. They were excluded from the complete case analysis, and their values imputed (see section 3.3.8 under Missing data).

<u>Linearity with the outcome</u>

Continuous measurements are often modelled in prediction models using a linear term, which assumes the effect of the predictor on the outcome is the same at each value of the predictor (231). However, it is possible that non-linear relationships between a predictor and the outcome exist. To assess for nonlinearity, restricted cubic spline (RCS) functions can be used (232). RCS functions are a type of cubic spline function which forces the tails to be linear. Splines require knots, at which the spline will bend around the knot. Commonly, three knot splines (two degrees of freedom) are used for small datasets, whilst five knot splines (four degrees of freedom) have been thought to capture most patterns of nonlinearity in larger datasets (233). Knots are defined from the quantiles of the dataset, and each successive increase in knots changes the location in quantiles.

Each continuous candidate predictor was assessed for its functional form (linear or non-linear) using three, four, and five knot splines (Appendix 3.4). Graphs were used to visualise the biological plausibility of the shape of each predictor with the log odds of the outcome. The Akaike's Information Criterion (AIC) was used to assess the likelihood ratio for the model in context of the degrees of freedom for each spline, with a lower AIC representing the best likelihood ratio for the model (233). A three-knot spline was chosen for age (knots are placed at the 10^{th}, 50^{th}, and 90^{th} percentiles (233)), as it was biologically plausible and had the lowest AIC. Linear formations were used for BMI, systolic blood pressure, and age at menarche.

3.3.8 Statistical analysis

All analyses were performed in R statistical software version 4.0.2, using the following packages (234): for data cleaning, coding and manipulation: plyr (235), dplyr (236), tidyr (237), DescTools (238); for data visualisation: ggplot2 (239), MASS (240); for sample size calculations: pmsampsise (241); for assessing missingness: naniar (242), VIM (243); for multiple imputation with chained equations (MICE): mice (244); for stacking multiple imputed datasets: reshape2 (245); for building the model: Hmisc (246), MASS (240), rms (247); for elastic net penalisation: caret (248); for calibration curves: pROC (249); for decision curve analysis: rmda (250).

A logistic regression model was developed, based on person-level data. To further guard against overfitting the data, elastic net penalisation was then applied (251). Elastic net is a penalisation method that combines the penalty factors (λ) of least absolute shrinkage and selection operator (LASSO) (termed $\alpha = 0$) and ridge (termed $\alpha = 1$) (252, 253). λ is the regularization term, and measures the size of the penalty factor, which controls the amount of shrinkage. A larger λ indicates more shrinkage and reflects the uncertainty of the model parameters before penalisation. LASSO penalises the regression coefficients of candidate predictors by a large λ, shrinking some of these coefficients to zero (231), and removing them from the model, working as a predictor selector (233, 252). Ridge-type regression method penalises the log likelihood for the model by a small λ, shrinking the regression coefficients of each candidate predictor by the same factor, so that no candidate predictor is removed from the model. The values of α and λ are chosen using 10-fold cross-validation (231). Cross-validation is a re-sampling technique. The dataset is split into *k* folds or groups (10 folds in the case of 10-fold cross-validation). One fold is used as a 'test' dataset, whilst the other k-1 folds are used as the 'training' dataset. To choose the optimal λ, for each possible value of λ the model is run on the ‘training’ dataset and then evaluated in the ‘test’ dataset to determine the model’s performance in the ‘test’ dataset. This is repeated for each ‘test’ dataset, giving a performance score for each fold, such that the model is trained using nine different folds and tested on one different fold each time, giving ten unique performance scores. The average of each performance score is taken to give the cross-validation score. This is repeated over a grid of values of λ. The λ value with the least cross-validation error is the optimal value of λ. A similar process is performed for α.

Regression coefficients and ORs (95% CIs) for each predictor were reported. As the model was fitted using elastic net regularisation (penalisation), overfitting was reduced by design. Therefore, further internal validation of the model was not required.

Model performance

The performance measures examined were discrimination and calibration. Discrimination is the ability of the model to differentiate participants with and without the event. It was quantified using the concordance (C)-statistic. The C-statistic is the probability that a model will give a higher risk for a participant with the outcome, compared to a participant without the outcome when this pair of participants is assessed together (254, 255). The C-statistic is equivalent to the area under the receiver operating characteristic curve, and lies between 0.5 (the model will correctly identify the participant with the outcome compared to the participant without the outcome in 50% of the times- i.e.- random concordance) and 1 (the model will always identify the participant with the outcome compared to the participant without it) (256, 257).

Calibration is the agreement between the predicted probabilities (the risk) and what was observed in the dataset (258). Calibration is visualised using a calibration plot, which plots the observed proportion of the outcome (y axis) against the prediction outcomes (x axis). If the observed and the predicted proportion of outcomes are entirely concordant, they fall along a 45° line on the calibration plot (174, 259), producing a calibration slope of 1. If the calibration slope is <1, this indicates the model is overfitted, and therefore the predictions from the model are too extreme (both too high for high risk participants, and too low for low risk participants). This can be due to a low sample size. A calibration slope of >1 indicates the model is underfitted, and therefore the predictions from the model are not extreme enough (i.e.- too modest) (predicted probabilities are not high enough for high probabilities, and not low enough for low probabilities) (260). This can be due to not including enough important risk factors in the model (261-263).

Nomogram

To enable clinical use of the prediction model, a nomogram was developed (233). A nomogram assigns a numerical point score to each predictor based on its importance in the model. For an individual patient or participant, their total numerical points, based on the combination of predictors they have, determines their individual predicted probability of the outcome. Being able to risk stratify patients based on their individual predictor values is an example of personalised medicine, a priority for the Commission of the Future of Surgery (67). A nomogram has been described as being one of the most appealing, accurate and discriminative methods of using a prediction tool in clinical practice (264).

Decision curve analysis

In this study, the aim of the prediction model is to identify participants who might develop incident IPJ osteoarthritis at 10 years' follow-up by calculating their individual risk. This could be compared to a clinical assessment to predict the same outcome. The theoretical clinical consequence of using a prediction model to predict an outcome (for example, using the model to predict the risk of incident IPJ osteoarthritis at 10 years), versus relying on how a clinician might traditionally assess a patient to predict the same outcome can be simulated using a decision curve (265). For participants who are identified as above a certain threshold (i.e.- high risk), they can often be identified without using a model. Similarly, participants below a certain threshold (i.e.-

low risk) are unlikely to require medical investigation or management, and so using the model might not be necessary. But for participants in between these two risk thresholds, the model may be useful in assessing their risk of disease.

For prediction models, a decision curve analysis assesses the benefit and the harms of using the prediction model, on the same scale, to calculate the net benefit (266). Net benefit can range from negative infinity to the incidence of the disease in the population (265). Therefore, it takes into account both the benefit of using the prediction model to predict the outcome, and also the risk of the model incorrectly identifying participants with the outcome (i.e.- predicting incident hand OA in someone who wouldn't actually go on to get the disease). This means that a decision curve analysis also takes into account both aspects of model performance , discrimination and calibration (267). The net benefit can be assessed at multiple risk thresholds. A risk threshold is a cut-off point after which a clinician might intervene- for example, the threshold for a patient after which a clinical assessment might be performed. Using the dataset, a data-driven approach can be used to set a risk threshold, and to minimise the number of misclassifications (false negatives and false positives) of the outcome (268). Through a decision curve analysis, multiple risk thresholds can be used to visualise net benefits. The formula for net benefit is (266):

$$\left(\frac{True\ positives}{Sample\ size} - \frac{False\ positives}{Sample\ size}\right) * \frac{Risk\ threshold}{1 - Risk\ threshold}$$

There are no established thresholds used clinically for the investigation and management of patients with IPJ osteoarthritis. Therefore, in this study, a range of net benefits was presented.

The net benefit can be equated to a cost:benefit ratio, for particular risk thresholds. The cost:benefit is the difference in cost, or utility, between a false negative and a false positive outcome (268). A data-driven approach can also be used to set cost:benefit thresholds using the calculation below (268):

$$(True\ positives - False\ positives) * \frac{Cost\ of\ false\ positives}{Cost\ of\ false\ negatives -\ Cost\ of\ true\ positives}$$

A reduction in the number of false positive diagnoses per 100 patients can also be calculated (265):

$$\frac{net\ benefit\ of\ model - net\ benefit\ of\ assessing\ all\ patients}{\frac{risk\ threshold}{1 - risk\ threshold}} * 100$$

On the same graph, a decision curve is also plotted to visualise the net benefit if no participants underwent clinical assessment for the outcome - for example, if no medical assessment was performed to assess the risk of IPJ osteoarthritis incidence; and a second decision curve is plotted for to visualise the net benefit if all patients underwent clinical assessment for the outcome.

To assess the possible clinical benefit of using the prediction model to identify patients at increased risk of IPJ osteoarthritis incidence at 10 years' follow-up, compared to performing clinical assessment on both everyone and no one, a decision curve analysis was performed. To correct the decision curve for overfitting the dataset, 10-fold cross-validation was used (269).

<u>Sensitivity analysis</u>

The developed model was evaluated to assess whether it was able to predict incident IPJ osteoarthritis in individuals with ≥2 IPJs with incident osteoarthritis, and then ≥3 IPJs with incident osteoarthritis. Calibration of the model (agreement between the predicted risks using the originally developed model, with the observed outcomes in the dataset used for sensitivity analysis) was assessed in ≥2 IPJs and ≥3 IPJs through visualisation of the calibration plot and the calibration slope, to determine any mis-calibration of the model.

If mis-calibration is seen, the results suggest there is systematic under- or over-estimation by the model in the dataset used for the sensitivity analysis. In this case, the model was re-calibrated through updating the intercept of the original model (262, 270, 271). This was done by calculating a correction factor, which assessed the frequency of the outcome in the dataset used for the sensitivity analysis with the mean predicted probability of the model (262):

$$\ln\left(\frac{\frac{observed\ outcome\ frequency}{1 - observed\ outcome\ frequency}}{\frac{mean\ predicted\ probability}{1 - mean\ predicted\ probability}}\right)$$

The correction factor was then added to the intercept of the original model, to give an updated intercept for the model.

The calibration curve was then re-fitted for the updated model, to give the ‘apparent’ calibration curve for the updated model.

The model was then internally validated using bootstrapping. Through bootstrapping, the model is fitted on the dataset, and then *B* bootstrap samples are then generated by resampling with replacement from the original dataset. At least 500 bootstrap samples are recommended (142), and in this case 2,000 bootstrap sample were used. A model is developed on each bootstrap sample, and the calibration curve of each bootstrap model in the corresponding bootstrap sample is produced. The mean difference (optimism) in the calibration curves over the 2,000 bootstrap samples is calculated, and this optimism is subtracted from the apparent calibration curve, to give an optimism-corrected calibration curve. As only the intercept has changed, and not the ordering of participants in the study, the C-statistic will be the same in the sensitivity analysis.

Sensitivity analysis was used for all participants who had complete data for predictors and the outcome.

Missing data

Both predictor and outcome data were examined for missingness. If missingness was found, missing data across multiple variables were visualised graphically to explore for patterns of missingness.

Patterns of missingness include missing not at random (MNAR), missing at random (MAR), and missing completely at random (MCAR). Values which are MNAR are due to the true values of the missing data, and again the population with missing data does not represent the population with complete data. Values which are MAR can be explained due to other variables, and therefore the population with missing data is not representative of the population with complete data. Values which are MCAR are not related to any participant characteristics, and could be due to random data input error, and the population with missing data is comparable to the population with complete data. Though the MCAR assumption cannot be tested, it can be assumed if MAR and MNAR patterns are not identified.

If ≤5% of data was missing, data on participants for which there was information on all candidate predictors and outcome was used (233, 272, 273). If >5% of data was missing, and missingness was shown to be either MCAR or MAR, MICE was used. If the data was MNAR, imputing is not advised as it can potentially skew the data imputation, as the imputed data is based on the data available in the dataset. For this study, the means and SDs of imputed data were checked for any trends, and imputed values were also compared with the original data to check for any patterns to the imputation. In the cases of ≤5% to 20% missing data, 20 iterations were used (i.e.- 20 imputed datasets were created) (274). In the case of ≥20% missing data, the number of iterations were equivalent to the percentage of missing data (i.e.- the equivalent number of imputed datasets were created). The model can then be run on each imputed dataset, resulting in multiple regression coefficients for each predictor (one from each dataset). The estimates from each imputed dataset can then be pooled (275). However, it can be difficult to pool results across imputed datasets if non-linear terms are used, as these might vary across the datasets. Instead, all of the imputed datasets can be 'stacked' into one dataset, excluding the original dataset with missing data (276). Continuous variables in the stacked dataset can then be assessed for linearity with the outcome using RCS functions, and the model can be run on the stacked dataset to provide one regression coefficient per predictor. Therefore, for this model, the 'stacked' dataset methodology was used.

In this study, there was no missing outcome data. However, 33 participants (7.2%) were missing predictor data: occupation (15 participants), systolic blood pressure (10 participants (including three which were outliers and biologically implausible, so coded as missing)), family history of knee osteoarthritis and family history of hand osteoarthritis (four participants), knee osteoarthritis (two participants), BMI (one participant), BMI, family history of knee osteoarthritis and family history of hand osteoarthritis (one participant) (Appendix 3.5a). No discernible patterns for missingness were observed (Appendix 3.5a), and the missing data was assumed to be MCAR. Participants with missing data, compared to those without missing data were less likely to work in manual occupation, less likely to have given birth to a live child/children, more likely to have experienced a miscarriage/ miscarriages, less likely to have had a hysterectomy, but more likely to have used the oral contraceptive pill and hormone replacement therapy, less likely to have smoked, less likely to have a family history of hand osteoarthritis, but more likely to have knee osteoarthritis and hand osteoarthritis (Appendix 3.5b). However, as the sample size of those with missing data was small, it is possible these are spurious findings.

Twenty imputed datasets were created, and no difference in the imputed data were observed (Appendix 3.6). The model was run using the imputed data, and a sensitivity analysis was also performed on participants who had complete data for all candidate predictors and the outcome (Appendix 3.7).

3.4 Results

3.4.1 Study participants

Participants without radiographs at baseline were comparable to participants with radiographs at baseline (Table 3.1). Of participants with radiographs at baseline, those without osteoarthritis at baseline (included in this study) compared to those with osteoarthritis at baseline (excluded from this study), were younger, less likely to have radiographic osteoarthritis in at least one first CMCJ, and less likely to have a self-reported family history of hand osteoarthritis (Table 3.1). Of participants included in this study, at baseline, median age was 51.0 (interquartile range (IQR): 9.0) years, with median BMI of 25.3 (IQR: 4.9) kg/m^2 (Table 3.1).

3.4.2 Candidate predictors

Participants with incident IPJ osteoarthritis at follow-up were more likely to work in manual occupations, and to have reached menopause, but less likely to have a history of using the oral contraceptive pill and hormone replacement therapy (Table 3.2). They were also more likely to have a radiographic osteoarthritis in at least one first CMCJ at baseline (Table 3.2).

Table 3.1: Demographics of participants with and without radiographs and with and without IPJ osteoarthritis at baseline in The Chingford 1000 Women Study

	No xrays at baseline n= 304	No OA at baseline n= 459	OA at baseline n= 206
Age (years) [median (IQR)]	56 (11)	51 (9)	58 (8.8)
BMI (kg/m^2) [median (IQR)]	26.2 (6.3)	25.3 (4.9)	26.7 (4.8)
Manual occupation [n (%)]			
Non-manual	242 (80)	365 (80)	156 (77)
Manual	57 (19)	79 (17)	41 (20)
OA at first CMCJ [n (%)]			
Yes	N/A	65 (14)	109 (54)
No		394 (86)	93 (46)
Family history of hand OA [n (%)]			
Yes	107 (35)	173 (38)	111 (55)
No	189 (62)	281 (61)	89 (44)

BMI: Body mass index; CMCJ: Carpometacarpal joint; IPJ: Interphalangeal joints; IQR: Interquartile range; OA: Osteoarthritis; Xray: Plain film radiograph
Osteoarthritis incidence was defined as KL grade ≥2 in ≥1 IPJ at follow up compared to baseline

Table 3.2: Distribution of candidate predictors in participants with and without incident IPJ osteoarthritis at follow-up in The Chingford 1000 Women Study

Predictor	All participants N=459	Participants without incident OA at follow up n= 257	Participants with Incident OA at follow up n= 202
Anthropometric features:			
1) Age (years) [median (IQR)]	51 (9)	50 (8)	52 (9)
Missing [n (%)]	0 (0)	0 (0)	0 (0)
2) Occupation [n (%)]			
Non-manual	365 (80)	211 (82)	154 (76)
Manual	79 (17)	35 (14)	44 (22)
Missing	15 (3)	11 (4)	4 (2)
3) BMI (kg/m^2) [mean(SD)]	26.03 (3.96)	25.79 (5.75)	26.27 (5.80)
Missing [n (%)]	2 (0.4)	2 (0.8)	0 (0)
4) Systolic blood pressure (mmHg) [mean(SD)]	124.4 (19.7)	122 (19.8)	126 (19.4)
Missing [n (%)]	7 (2)	1 (0.4)	6 (3)
5) History of hand fracture [n (%)]			
No	453 (99)	253 (98)	200 (99)
Yes	6 (1)	4 (2)	2 (1)
Missing	0 (0)	0 (0)	0 (0)
Female hormonal factors:			
6) Age at menarche (years) [median (IQR)]	13 (2)	13 (2)	13 (2)
Missing [n (%)]	0 (0)	0 (0)	0 (0)
7) Reached menopause [n (%)]			
No	151 (33)	93 (36)	58 (29)
Yes	308 (67)	164 (64)	144 (71)
Missing	0 (0)	0 (0)	0 (0)
8) Live births [n (%)]			
No	62 (14)	36 (14)	26 (13)
Yes	397 (86)	221 (86)	176 (87)
Missing	0 (0)	0 (0)	0 (0)
9) Miscarriage [n (%)]			
No	302 (66)	168 (65)	134 (66)
Yes	157 (34)	89 (35)	68 (34)
Missing	0 (0)	0 (0)	0 (0)
10) Hysterectomy [n (%)]			
No	358 (78)	197 (77)	161 (80)
Yes	101 (22)	60 (23)	41 (20)
Missing	0 (0)	0 (0)	0 (0)
11) Use of oral contraceptive pill [n (%)]			
No	273 (59)	141 (55)	132 (65)
Yes	186 (41)	116 (45)	70 (35)
Missing	0 (0)	0 (0)	0 (0)

12) Use of hormone replacement therapy [n (%)]			
No	350 (76)	189 (74)	161 (80)
Yes	109 (24)	68 (26)	41 (20)
Missing	0 (0)	0 (0)	0 (0)
Smoking and alcohol history:			
13) Smoking [n (%)]			
Never	256 (56)	146 (57)	110 (54)
Ever	203 (44)	111 (43)	92 (46)
Missing	0 (0)	0 (0)	0 (0)
14) Alcohol use [n (%)]			
Never	62 (14)	36 (14)	26 (13)
Ever	397 (86)	221 (86)	176 (87)
Missing	0 (0)	0 (0)	0 (0)
Family history:			
15) History of knee osteoarthritis in family [n (%)]			
No	232 (51)	124 (48)	108 (53)
Yes	222 (48)	130 (50)	92 (46)
Missing	5 (1)	3 (1)	2 (1)
16) History of hand osteoarthritis in family [n (%)]			
No	281 (61)	154 (60)	127 (63)
Yes	173 (38)	100 (39)	73 (36)
Missing	5 (1)	3 (1)	2 (1)
History of osteoarthritis at other joints:			
17) Osteoarthritis in ≥1 knee joint (KL≥2) [n (%)]			
No	414 (90)	234 (91)	180 (89)
Yes	43 (9)	23 (9)	20 (10)
Missing	2 (1)	0 (0)	2 (1)
18) Osteoarthritis in ≥1 first CMCJ (KL≥2) [n (%)]			
No	394 (86)	230 (89)	164 (81)
Yes	65 (14)	27 (11)	38 (19)
Missing	0 (0)	0 (0)	0 (0)

BMI: Body mass index; CMCJ: Carpometacarpal joint; IPJ: Interphalangeal joints; IQR: Interquartile range; KL: Kellgren Lawrence; OA: Osteoarthritis; SD: Standard deviation; Xray: Plain film radiograph

Osteoarthritis incidence was defined as KL grade ≥2 in ≥1 IPJ at 10 years' time from when the nomogram was used

3.4.3 The model

In the elastic net penalisation, an α = 0.1 and a λ = 0.01 (closer to LASSO than ridge) were found to be optimal and were used to fit the model. Using the elastic net, all predictors were retained in the model and no regression coefficients were shrunk to zero.

The model showed that manual versus non manual occupation (OR: 1.70, 95% CI: 1.08 to 3.09), and a history of radiographic osteoarthritis in at least one first CMCJ (OR: 1.76, 95% CI: 1.06 to 3.30) were important predictors for incident IPJ osteoarthritis at follow-up (Table 3.3). As age was modelled using a three-knot spline, the effect measure is difficult to interpret, and instead it can be visualised graphically (Figure 3.3). The graph shows that as age increases up to 57 years, the risk of incident IPJ osteoarthritis increases, and then starts to plateau and slightly decrease (Figure 3.2).

The equation for the model is:

$$\log(odds) = logit\ (incident\ IPJ\ OA) = log\frac{P}{1-P} = LP$$

Where $LP = -3.68 + 0.05\ (50th\ percentile\ of\ age) - 0.04\ (90th\ percentile\ of\ age) +$

$0.53\ (manual\ occupation) + 0.01\ (BMI) + 0.01\ (systolic\ blood\ pressure) -$

$0.22\ (history\ of\ hand\ injury) - 0.07\ (age\ at\ menarche) + 0.04\ (post\ menopausal) +$

$0.01\ (\geq 1\ live\ births) - 0.03\ (\geq 1\ miscarriages) - 0.08\ (had\ hysterectomy) -$

$0.20\ (used\ oral\ contraceptive\ pill) - 0.34\ (used\ hormone\ replacement\ theraoy) +$

$0.20\ (ever\ smoked) + 0.24\ (ever\ drunk\ alcohol) - 0.20\ (family\ history\ of\ knee\ osteoarthritis) -$

$0.02\ (family\ history\ of\ hand\ osteoarthritis) - 0.09\ (osteoarthritis\ in \geq 1\ knee) +$

$0.56\ (Osteoarthritis\ in \geq 1\ first\ CMCJ)$

With a participant’s individual probability of incident IPJ osteoarthritis at 10 years’:

$$P = \frac{\exp(LP)}{1 + exp\ (LP)}$$

IPJ: Interphalangeal joint

OA: Osteoarthritis

P= Proportion of incident interphalangeal joint osteoarthritis

Model performance

The $R^2_{Nagelkerke}$ was 0.02. The discrimination of the model was acceptable (C-statistic: 0.66, 95% CI: 0.64 to 0.67), but the model was mis-calibrated (calibration slope: 1.12, 95% CI: 1.03 to 1.21) (Figure 3.3).

Results from running the model in complete case data can be found in Appendix 3.7. Using the complete case data, the elastic net removed history of hand fractures and history of miscarriages from the model.

Table 3.3: Coefficients, standard errors, p values and odds ratios for the prediction model for incident IPJ osteoarthritis

Predictor	B coefficient	Standard error	p value	Odds ratio	95% CI
Intercept	-3.68	3.23	0.03	0.03	0.000014 to 0.43
Age (years): RCS: Knot 2	0.05	0.07	0.05	1.06	1.00 to 1.30
Knot 3	-0.04	0.09	0.11	0.96	0.73 to 1.03
Occupation	0.53	0.27	0.03	1.70	1.08 to 3.09
BMI (kg/m^2)	0.01	0.03	0.57	1.01	0.96 to 1.07
BP systolic	0.01	0.01	0.13	1.01	1.00 to 1.02
Hand fracture	-0.22	0.92	0.74	0.80	0.12 to 4.41
Age at menarche	-0.07	0.06	0.17	0.93	0.81 to 1.04
Menopause	0.04	0.31	0.80	1.04	0.50 to 1.69
Live births	0.01	0.30	0.97	1.01	0.56 to 1.84
Miscarriages	-0.03	0.22	0.89	0.98	0.64 to 1.48
Hysterectomy	-0.08	0.27	0.76	0.92	0.54 to 1.58
Oral contraceptive pill	-0.20	0.22	0.37	0.82	0.53 to 1.27
Hormone replacement therapy	-0.34	0.25	0.11	0.71	0.41 to 1.10
Smoking	0.20	0.21	0.22	1.22	0.86 to 1.93
Alcohol use	0.24	0.30	0.39	1.26	0.72 to 2.01
Family knee OA	-0.20	0.22	0.32	0.82	0.52 to 1.24
Family hand OA	-0.02	0.23	0.87	0.98	0.61 to 1.51
OA Knee	-0.09	0.35	0.72	0.91	0.45 to 1.76
OA CMCJ	0.56	0.29	0.03	1.76	1.06 to 3.30

95% CI: 95% confidence interval; BMI: Body mass index; BP: Blood pressure; CMCJ: Carpometacarpal joint; OA: Osteoarthritis; RCS: Restricted cubic spline (age was modelled using a three knot term)

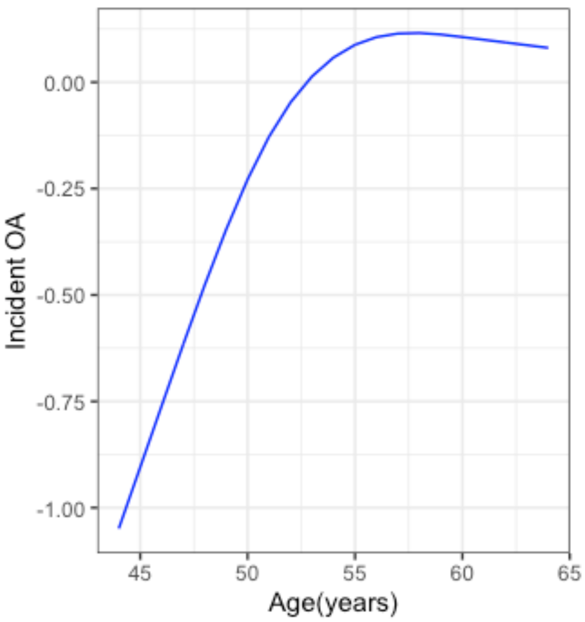

Figure 3.2: Relationship between increasing age and the log odds risk of incident IPJ osteoarthritis

Osteoarthritis incidence was defined as KL grade ≥2 in ≥1 IPJ at follow up compared to baseline

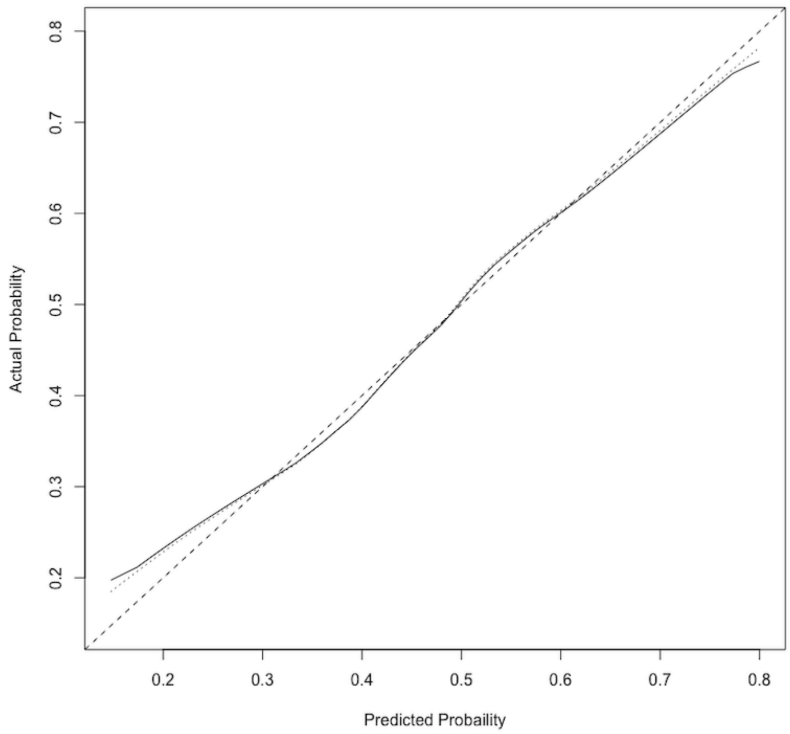

Figure 3.3: Calibration plot of the prediction model for incident IPJ osteoarthritis

X axis: Predicted probability from the model
Y axis: Actual probability from the dataset
The dashed line (45° angle) represents perfect calibration.
The dotted line represents calibration of the model before correcting for overfitting.
The continuous line represents calibration of the model after correcting for overfitting through elastic net penalization.

Nomogram

The nomogram based on the model showed that a total score of 590 corresponds to a >95% risk of a participant developing incident IPJ osteoarthritis in 10 years' time (Figure 3.4). Based on the model, a participant would have almost 100% risk of incident IPJ osteoarthritis at 10 years, if, at the time the nomogram was used, they were aged between 54 to 56 years, worked in manual occupation, were morbidly obese (BMI $\geq$50kg/m^2), with a systolic blood pressure of 180mmHg, with a history of hand fracture experienced menarche at age 9 years, had not yet experienced menopause, had live birth/s and no miscarriages, had not had a hysterectomy or used the oral contraceptive pill or hormone replacement therapy, but had smoked and drunk alcohol, did not have a family history of either knee or hand osteoarthritis, did not themselves have knee osteoarthritis, but did have osteoarthritis in at least one first CMCJ.

The nomogram shows that the largest contributors to points are age between 54 to 56, manual occupation, high systolic blood pressure, young age at menarche, and osteoarthritis in at least one first CMCJ.

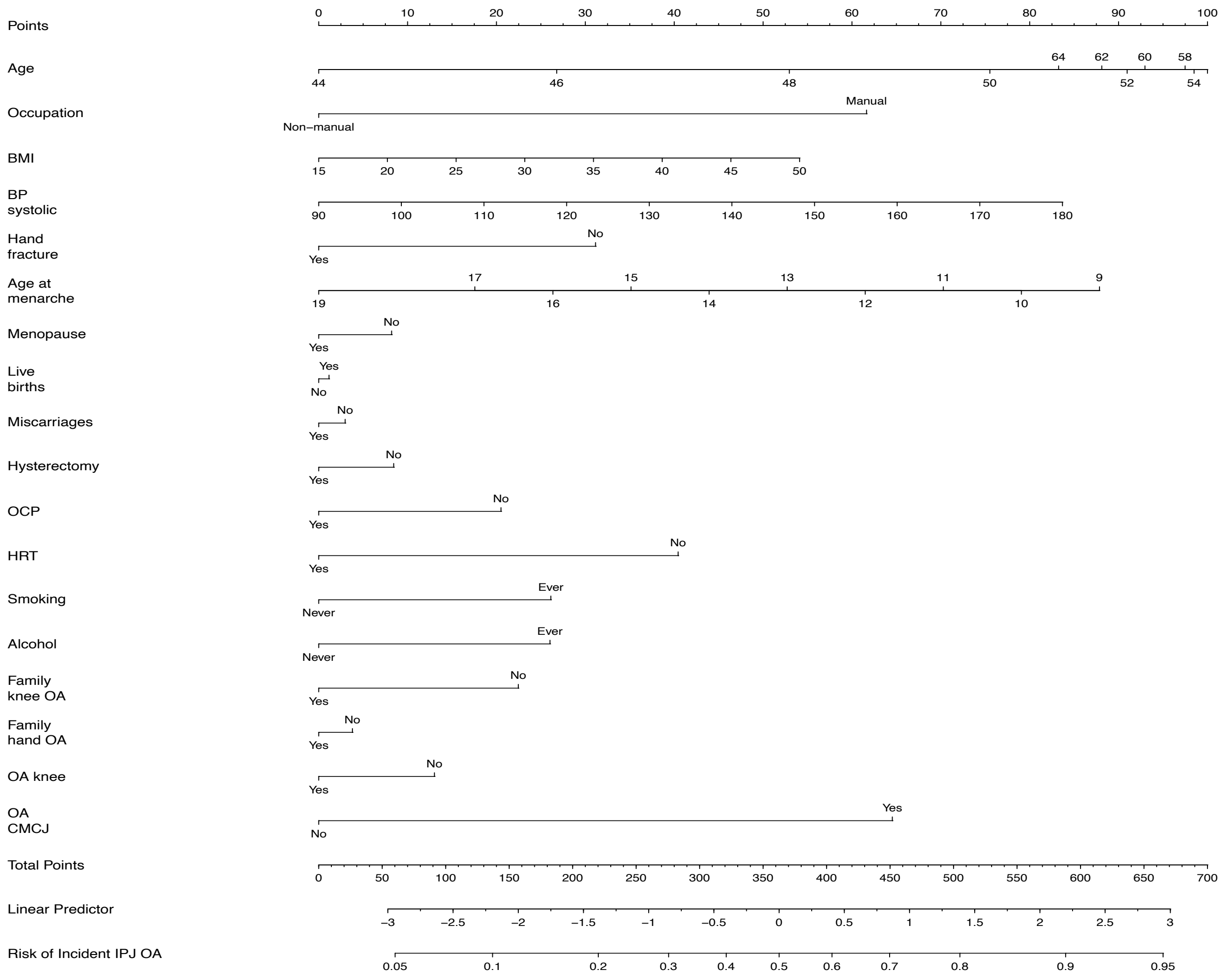

Figure 3.4: Nomogram to predict incident IPJ osteoarthritis

BMI: Body mass index; BP: Blood pressure; CMCJ: Carpometacarpal joint; HRT: Hormone replacement therapy; OA: Osteoarthritis; OCP: oral contraceptive pill
Osteoarthritis incidence was defined as KL grade ≥2 in ≥1 IPJ at 10 years' time from when the nomogram is used

Decision curve

The net benefit of both the prediction model and all patients undergoing clinical assessment to predict incident IPJ osteoarthritis at 10 years' follow-up is similar up to a risk threshold of approximately 40% (Figure 3.5).

Below a risk threshold of 40%, the model is not very accurate (high false positives). At a risk threshold of 40%, for every 100 patients, the model prevents unnecessary clinical assessment in three patients compared to assessing all patients, and a reduction of five false positives (Table 3.4). At this point, the benefit of using the model outweighs its cost (cost:benefit of 2:3) (Figure 3.5, Table 3.4). At a risk threshold of 50%, the prediction model prevents unnecessary clinical assessment in 28 out of 100 patients, and a reduction of 28 false positives per 100 patients (Table 3.4). At this risk threshold, the cost:benefit is equalised, and after this risk threshold the cost is greater than the benefit (Figure 3.5).

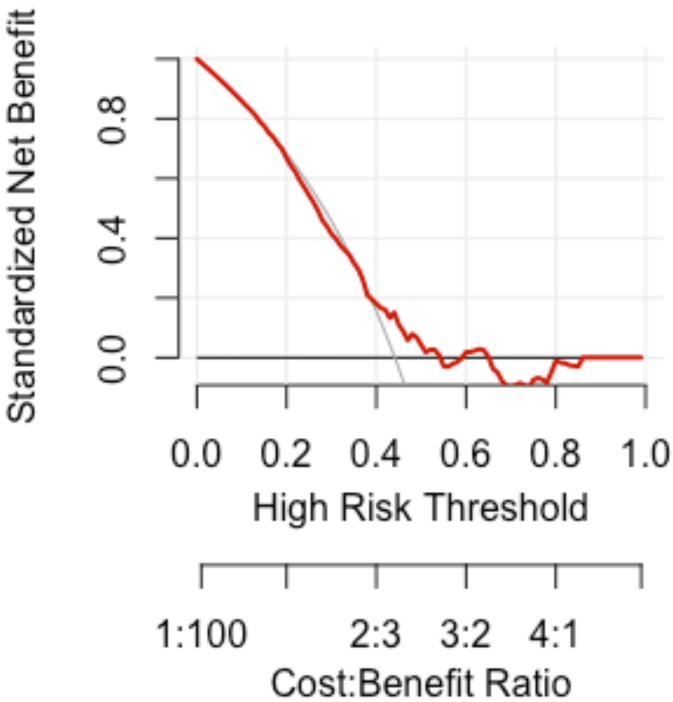

Figure 3.5: Decision curve analysis of the prediction model versus assess all and assess none for incident IPJ osteoarthritis

The grey curve representing clinically assessing all patients regardless of their risk**.**
The red curve represents using the prediction model to assess all patients regards of their risk
Risk threshold refers to the risk of developing incident interphalangeal joint osteoarthritis at 10 years' follow-up
Cost:Benefit ratio refers to the costs (or utility) between a false negative and a false positive outcome (268)
The net benefit refers to the benefit and the harms on the same scale

Table 3.4: Net benefit of the prediction model versus assess all and assess none for incident IPJ osteoarthritis

Risk threshold (%)	Cost:benefit	Net benefit			Difference in net benefit between assessing all and using the model	Reduction in false positive diagnoses per 100 patients
		Assess all	Use model	Assess none		
0	0:1	1	1	0	0	n/a
5	1:19	0.93	0.93	0	0	0
10	1:9	0.86	0.86	0	0	0
15	3:17	0.78	0.78	0	0	0
20	1:4	0.68	0.67	0	-0.01	-4
25	1:3	0.58	0.53	0	-0.05	-15
30	3:7	0.46	0.40	0	-0.06	-14
35	7:13	0.32	0.27	0	-0.05	-9
40	2:3	0.16	0.19	0	0.03	5
45	9:11	-0.04	0.09	0	0.13	16
50	1:1	-0.27	0.01	0	0.28	28

Risk threshold refers to the risk of developing incident interphalangeal joint osteoarthritis at 10 years' follow-up
Cost:Benefit ratio refers to the costs (or utility) between a false negative and a false positive outcome (268)
The net benefit refers to the benefit and the harms on the same scale (268)
Reduction in the number of false positive diagnoses per 100 patients (265)

Sensitivity analyses

a) Incident osteoarthritis in ≥2 IPJs

In the sensitivity analysis for ≥2 IPJs with incident osteoarthritis, from 426 participants in the dataset, 74 developed incident osteoarthritis in only one IPJ at follow-up, and were excluded. Therefore, 352 participants remained in the subgroup. Out of these, 114 (32.4%) participants developed incident IPJ osteoarthritis in ≥2 joints at follow-up. When the model was evaluated to assess whether it was able to predict incident IPJ osteoarthritis in individuals with ≥2 IPJs with incident osteoarthritis, it was mis-calibrated (Figure 3.6a) (calibration slope: 1.25). Following re-calibration through updating the intercept of the original model, (correction factor: -0.48) the calibration slope showed improvement (Figure 3.6b).

b) Incident osteoarthritis in ≥3 IPJs

In the sensitivity analysis for ≥3 IPJs with incident osteoarthritis, from 426 participants in the dataset, 122 developed incident osteoarthritis in one or two IPJs at follow-up, and were excluded. Therefore, 304 participants remained in the subgroup. Out of these, 66 (21.7%) participants developed incident IPJ osteoarthritis in ≥3 joints at follow-up. When the model was evaluated to assess whether it was able to predict incident IPJ osteoarthritis in individuals with ≥3 IPJs with incident osteoarthritis, it was mis-calibrated (Figure 3.7a) (calibration slope: 1.43). Following re-calibration through updating the intercept of the original model (correction factor: -1.56), the calibration slope showed improvement (Figure 3.7b).

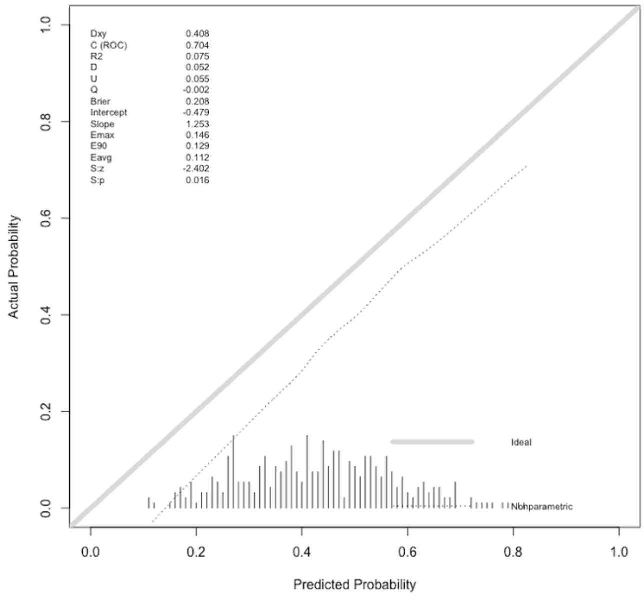

Figure 3.6a

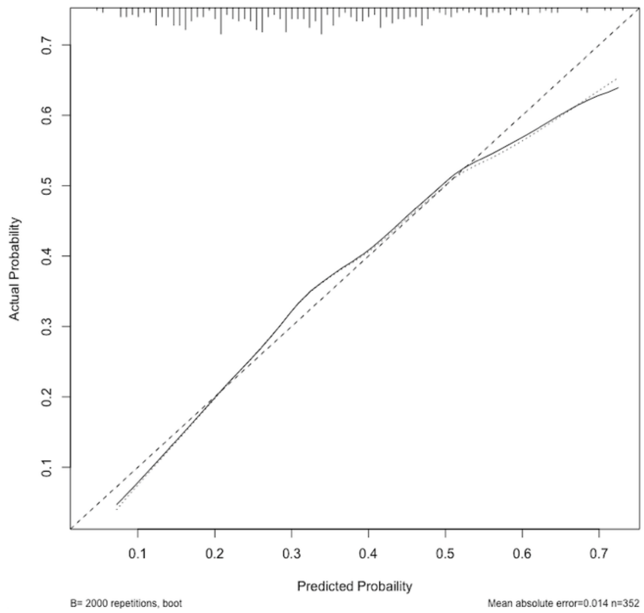

Figure 3.6b

Figure 3.6: Calibration plots of model in subgroup for ≥2 IPJs with incident osteoarthritis

a)Calibration plot when the original model was evaluated in the subgroup;
b)Calibration plot after model was updated
X axis: Predicted probability from the model
Y axis: Actual probability from the dataset
The dashed line (45° angle) represents perfect calibration.
The dotted line represents the apparent calibration of the model before correcting for overfitting.
The continuous line represents the optimism-corrected calibration of the model after internal validation with 2,000 bootstrap iterations.

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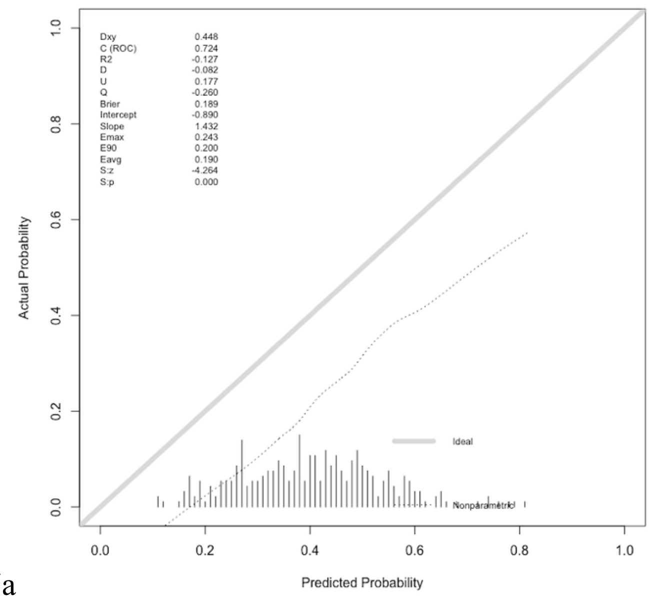


Figure 3.7a

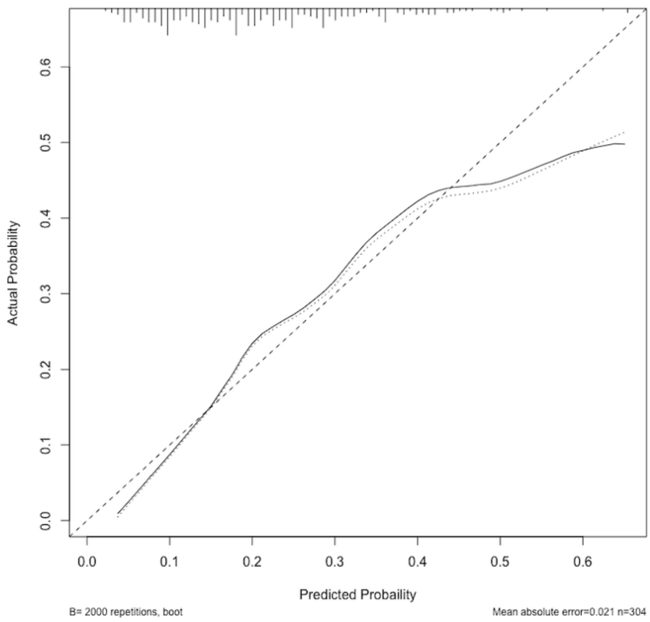


Figure 3.7b

Figure 3.7: Calibration plots of model in subgroup for ≥3 IPJs with incident osteoarthritis

a)Calibration plot when the original model was evaluated in the subgroup;
b)Calibration plot after model was updated
X axis: Predicted probability from the model
Y axis: Actual probability from the dataset
The dashed line (45° angle) represents perfect calibration.
The dotted line represents the apparent calibration of the model before correcting for overfitting.
The continuous line represents the optimism-corrected calibration of the model after internal validation with 2,000 bootstrap iterations.

3.5 Discussion

3.5.1 Summary

A logistic regression model was built for incident IPJ osteoarthritis at 10 years' follow-up from the Chingford Study. The model found that older age, manual occupation and osteoarthritis in at least one first CMCJ are all important predictors for incident IPJ osteoarthritis. Performance of the model showed acceptable discrimination (C-statistic 0.66 (95% CI: 0.64 to 0.67): and some mis-calibration (calibration slope: 1.12, 95% CI: 1.03 to 1.21). Using the model was also found to have a higher net benefit than assessing all patients or assessing no patients.

Both the imputed and completed case versions of the prediction model showed good discrimination. One prediction model has previously been built for incident hand osteoarthritis, in a population of young men. It showed a discrimination (C-statistic) of 0.62 (95% CI: 0.58 to 0.64) (210). Updating of that model in a population of women reported a discrimination of 0.62 (95% CI: 0.59 to 0.64) (211). The discrimination of the model built in this thesis chapter has better discrimination then the two published models (210, 211), suggesting it is more accurate in detecting the outcome. Though, it is difficult to directly compare the model performances to each other, as they have not been evaluated in the same data.

In a prediction model built in the Chingford Study for incident knee osteoarthritis at 10 years' follow-up, discrimination was between 0.56 to 0.70 (277). In the model for knee osteoarthritis, higher discriminative values were found when baseline predictors included radiographic hand or hip osteoarthritis (277). In the current model, despite radiographic knee and first CMCJ osteoarthritis being including as baseline predictors, discrimination stayed below 0.7. This suggests that hand osteoarthritis might be an important predictor for knee osteoarthritis (277), but knee osteoarthritis is not an important predictor for IPJ osteoarthritis. This could be because the peak age for incident hand osteoarthritis is approximately 10 years younger than the peak age for incident knee osteoarthritis (26). It also suggests that osteoarthritis at these different sites could be different phenotypes, with different predictors, aetiology, and pathophysiology. In particular, high BMI and acute traumatic injury are known to be strong predictors for knee and hip osteoarthritis (278-280), but were not found to be strong risk factors for IPJ osteoarthritis in the model.

In this study, the calibration slope of the model was higher than of the previously published models (210, 211). The calibration slope was >1, indicating the predicted outcomes were not extreme enough, and that the model is not predicting enough people with incident IPJ osteoarthritis. Penalisation of small datasets can sometimes lead to worsening model performance, due to the uncertainty surrounding the tuning parameters of the shrinkage mechanism (281). To prevent this, the model without elastic net penalisation could be used. However, in this study, the calibration plot improved after elastic net penalisation, suggesting penalisation was useful.

The model built from the complete data showed some mis-calibration at the tails of the calibration plot. The plot demonstrated that when the actual probability of incident osteoarthritis was low, the model under-predicted this, and when the actual probability of incident osteoarthritis was high, the model over-predicted this. This could be due to few participants with such extreme actual probabilities, resulting in poor fitting of the model at the extremes. This may be improved by increasing sample size.

Age was found to be an important predictor of incident IPJ osteoarthritis. Participants recruited to the Chingford Study at baseline were between the ages of 45 to 64 years, and therefore age could only be modelled across these years. Participants in this study were also younger (median age 51 years) compared to those excluded from this study due to having baseline radiographic IPJ osteoarthritis (median age 58 years). The results showed that as age increased up to 57 years, the risk of incident IPJ osteoarthritis increased. The risk then started to slowly decrease, as age continued to increase. This suggests that the incidence of radiographic IPJ osteoarthritis peaks in the late 50s age group. This is similar to results found in a study of the progression of hand osteoarthritis over two years, measured using the OARSI atlas, which reported that women in ≤10 years post-menopause were at higher risk of disease progression, compared to those who had been post-menopausal for >10 years (96).

In the systematic review (Chapter 2), older age was found to be a predictor for radiographic incident IPJ osteoarthritis in women (134, 137, 138, 168). However, these studies did not model age using non-linear transformation, so were unable to capture any changes of risk with age, if they did exist (134, 137, 138, 168). In patients who are diagnosed with incident hand osteoarthritis after presenting to healthcare, the peak incidence in women is reported between the ages of 60 to 75 years' old (26). These patients were identified through ICD-10 codes in Spain (26). Similarly, the peak incidence of symptomatic hand osteoarthritis in women in the US has been reported at between 70 to 79 years' old (282), and in those seeking treatment for hand osteoarthritis, the peak incidence in women in the UK is aged between 65 to 74 years (185).

Our study findings suggest that incident IPJ osteoarthritis might occur in a slightly younger age group than reported for hand osteoarthritis in the literature. This could be because patients studied in the literature were identified using hospital-based diagnoses and symptomatic criteria. This could cause an ascertainment bias, as there might be a time lag between people developing osteoarthritis (which could be identified radiographically), and presenting to health-care facilities for management. The decrease in risk in the higher age groups could also be due to low frequency of participants in the higher age range, preventing stable modelling of age across the higher age range, and, to better understand the role of increasing age on radiographic incident IPJ osteoarthritis, participants within a larger age range should be included in future studies.

Manual occupation was also found to be an important predictor of incident IPJ osteoarthritis. Historically, hand osteoarthritis has been associated with those working as cotton spinners and textile workers (283, 284). The development of osteoarthritis in this population is likely due to repetitive load being applied across the hand joints, resulting in repetitive microtrauma at these joints (92). In the knee, repetitive loading has been associated with osteoarthritis. This is thought to be due to repetitive mechanical loading, which in animal models can cause chondrocyte death and cartilage degeneration (285, 286). A similar mechanism might occur in hand joints that experience multiple cycles of loading. However, my systematic review (Chapter 2) found mechanical stress in women (137) and dental occupation in women (164), were not predictors for radiographic IPJ osteoarthritis. This suggests that manual occupation might only be a predictor for incident IPJ osteoarthritis when multiple other predictors are incorporated into the analysis, such as in this prediction model. It could also be because data in this prediction model was taken from the Chingford Study, which collected highly granular information on the occupation of participants. Though, this data was then collapsed into two variables for the model (manual or non-manual occupations), the use of granular data is likely to have increased the accuracy of the predictors used in this model.

It is possible that in my prediction model manual occupation might also represent an increased incidence and prevalence of joint trauma. Though a history of hand fracture was also included in the model, it was removed from the analysis with complete data, after elastic net. This suggests that either hand fracture is not an important predictor for incident IPJ osteoarthritis, or the prevalence of hand fracture was too low in this population for it to be accurately modelled. It is more likely that the prevalence of hand fracture was too low for the model to assess it (the prevalence of hand fracture in the participants included from the Chingford Study was just 6%), leading to a spurious result. Therefore, later stages of this thesis investigate the association between hand injury and hand osteoarthritis (Chapter 5).

Radiographic first CMCJ osteoarthritis was also an important predictor for incident radiographic IPJ osteoarthritis. This suggests that once radiographic osteoarthritis develops in any one of the first CMCJs, the risk of osteoarthritis developing in any finger IPJ is increased. This could be due to the presence of the same pathophysiological factors causing disease at both joint types, such as genetic causes. It could also be due to a direct relationship between osteoarthritis at the first CMCJ causing a change in force and loading across the hand, leading to osteoarthritis at an IPJ. Of note, in those with radiographic IPJ OA at baseline, 46% did not have any evidence of first CMCJ osteoarthritis. This suggests that whilst there may be a relationship between first CMCJ OA and IPJ OA, the direction and magnitude of the relationship remains unclear. A cluster analysis of radiographic incident osteoarthritis across different hand joints has shown a relationship between osteoarthritis at the first CMCJs and the finger IPJs, though, the relationship is likely to be limited, with the distance between first CMCJ osteoarthritis and IPJ osteoarthritis being far apart on a tree diagram (168). I plan to investigate the relationship between IPJ and first CMCJ osteoarthritis, considering both change in force across the hand following first CMCJ osteoarthritis, and the importance of systematic predictors, through a future National Institute of Health grant application, in collaboration with Wake Forest University. Furthermore, in Chapter 5 of this thesis I consider first CMCJ and IPJ osteoarthritis as one disease, in the form of a composite outcome of hand osteoarthritis (in part owing to the necessity of using routinely collected data that did not distinguish the two entities).

No female hormonal factors were found to be associated with incident IPJ osteoarthritis in the prediction model. This supports evidence from my systematic review, in which female hormonal factors were generally found not to be predictors for radiographic IPJ osteoarthritis (Chapter 2). In the systematic review, only parity was found to be a predictor for radiographic incident IPJ osteoarthritis, and the evidence was limited (167). Similarly, the incidence of radiographic osteoarthritis in the hand in general has not been found to have an association with female hormonal factors in a case control study (287). Using the Chingford Study, a cross-sectional analysis has also been performed for the association between ever using (>12 months) versus never using hormone replacement therapy (HRT), and between currently using (>12 months) versus never using HRT, in post-menopausal women (288), despite hand osteoarthritis most commonly occurring in peri-menopausal women. Neither variable were found to be associated with radiographic DIPJ osteoarthritis (KL ≥2 in ≥1 DIPJ) (288). Within the prediction model, these predictors were all assessed in a binary manner. It is possible that more granular data, such as using continuous variables (for example, the number of years HRT has been used for, or the number of live births), might have captured an association if one exists. But, in order to maximise the sample size and minimise the degrees of freedom in this prediction model, binary variables were used.

There was no association between metabolic predictors (BMI or systolic blood pressure) or smoking and alcohol, and incident IPJ osteoarthritis, supporting resulting from the systematic review in Chapter 2. This contrasts with a prediction model for incident hand osteoarthritis after 40 years, defined using ICD-10 codes for both the first CMCJ and the IPJs, in Swedish men (210). The prediction model for men found lifestyle-related factors (smoking, high alcohol intake, sports participation, fitness, and BMI) were important predictors for incident hand osteoarthritis. However, that model included all hand joints, defined osteoarthritis clinically, selected predictors using backward selection, and assessed young men, who are known to have a low prevalence of hand osteoarthritis (26). It is also possible that these lifestyle factors vary between men and women, and may present at higher levels in men, causing an effect on osteoarthritis.

3.5.2 Potential limitations

<u>Limitations with study population</u>

The Chingford Study, a population-based study, was used as the results should be generalisable to similar members of the general population. Recruitment of the Chingford Study showed a 78% response rate, and study participants have been described as being representative of the UK population at the time (224, 225). However, more recent data is unavailable to compare the current UK population to the women recruited to the Chingford Study. In particular, the 2011 UK Census described 3.4% of the population as being of ‘Black/ African/ Caribbean/ Black British’ race, whilst this is not captured in the Chingford Study (289). Therefore, it is possible the model does not accurately reflect the current population.

Participants were included in this study if they had both hand radiographs at baseline and 10-year follow-up, and had no evidence of IPJ osteoarthritis on baseline radiographs. Approximately one third of participants did not have baseline radiographs. Of participants who did have baseline radiographs, one third already had IPJ osteoarthritis at baseline. Therefore, the number of participants included in this study was smaller than expected. Participants included in the study were younger, less likely to have osteoarthritis in at least one first CMCJ, and less likely to have a family history of hand osteoarthritis. This might have biased the results away from age, first CMCJ osteoarthritis, and family history of hand osteoarthritis being identified as important predictors for incident IPJ osteoarthritis in the model. As the results showed that older age and first CMCJ osteoarthritis were important predictors, it is likely that the effect of these predictors is strong, though the extent of this may not have been captured.

Limitations with data variables

Data was captured in the Chingford Study primarily using self-reported questionnaires. The reliability of this data capture tool has not yet been assessed in the Chingford Study. It is possible that there could be recall bias. This is particularly important for events which occurred a long time in past, as there is known to be more under-estimation of events as time periods increase (290). Similarly, family history questions related to multiple members of the family, including those outside the nuclear family. It is possible that participants might not be able to accurately describe the burden of osteoarthritis across several more distant family members (such as maternal aunt). To account for this, the predictor for family history was developed into a composite variable, taking into account a history of hand osteoarthritis in at least one of multiple family members. This also allowed for the degrees of freedom in the model to be minimised.

The predictors were only assessed at baseline for this model. The model did not take into account any changes to predictor values over time (for example, changing BMI). This is particularly pertinent for modifiable predictors, such as smoking, which might change over time. Repeated measurements of predictors are currently not commonly incorporated when developing prediction models. This is because the methodology is not yet well established and computationally burdensome. There also needs to be an adequate time interval between the exposure to the predictor and the outcome. However, to more accurately reflect the behaviours of the general population, and the effect of changes to predictors, mixed-effects models could be used in studies which capture these changes.

Systolic blood pressure was one of the four continuous candidate predictors. It was the only candidate predictor found to have outliers which were not considered to be biologically plausible (readings of 200mmHg, 210mmHg, and 230mmHg), and therefore coded as missing data. These three readings would be of concern in primary care, as a blood pressure of ≥180/120mmHg would be considered as severe hypertension, requiring immediate emergency investigation and management (291). It is possible that these three study participants had high readings due to 'white coat syndrome' (292). Coding these three values as missing contributed to the amount of missing data. In this model, systolic blood pressure was measured as a continuous variable. However, if it has been measured as a categorical a variable, coding these three high blood pressure readings as missing would have biased the association between blood pressure and the risk of incident IPJ osteoarthritis towards the null, particularly if there was a threshold effect. This type of bias is less likely to exist in this model, by keeping blood pressure as a continuous variable, and testing different transformations through restricted cubic splines.

History of hand fracture was a candidate predictor in the model. However, the prevalence of participants having a history of hand fracture was only 6%. This was much lower than the prevalence of any other candidate predictors in the model. Using a binary candidate predictor with low prevalence has been shown to increase the chance of both complete and quasi separation in a logistic regression model (293, 294). Separation occurs when the value of the outcome variable is perfectly determined by the predictor variable. In quasi-separation, a 2x2 table would show a cell with no values. This can also lead to large standard errors, as seen in the model built with MICE. In the model built from complete case data, a history of hand fracture was removed from the elastic net (i.e.- β coefficient of 0), which could be due to the low prevalence of participants having a hand fracture. In my systematic review, a history of finger fracture was found to be a predictor for the incidence of IPJ osteoarthritis (167) (Chapter 2).To better analyse the possible relationship between hand injuries, such as fracture, and osteoarthritis, I have conducted a different kind of study in Chapter 5 of this thesis.

Occupation was reduced to a binary candidate predictor in the model. However, this could result in misclassification of some data. For example, study participants who identified as being housewives were classified as having 'non-manual' occupation, though it is possible they performed manual household tasks, such as cleaning. From the Chingford Study, there was also no further information on how long a participant had worked in their current occupation. In particular, 'retired' was a response option, yet this did not take into account for how long a participant had been retired and what was their primary occupation prior to retirement. It is possible that a longer history of manual occupation might increase the loading of the finger joints, and the associated microtrauma, leading to osteoarthritis. It is also possible that socioeconomic status could affect the relationship between manual occupation and IPJ osteoarthritis, though this was not captured in the Chingford Study and therefore could not be considered in the model. In the future, epidemiological studies should consider the length of time a participant had worked in a particular occupation and their socioeconomic status, to better capture the potential period of joint loading and repetitive microtrauma.

My systematic review identified no consensus criteria for defining incident IPJ osteoarthritis (Chapter 2). However, it did find that radiographs were most commonly used to classify incident IPJ osteoarthritis, with the threshold being set at KL ≥2 (Chapter 2). Incident osteoarthritis was classified as KL ≥2 in ≥1 IPJ. This is a wide definition, and might have decreased the discriminative ability of the model. To assess the use of more strict thresholds, sensitivity analyses were performed. The model required re-calibration in the subgroups, and, following this, the calibration improved. This suggests that a more specific outcome based on a higher number of IPJs with osteoarthritis would likely have improved the performance of the model.

This prediction model measured the osteoarthritis radiographically, using the KL atlas (80). The inter-reader kappa correlations were high for the two radiograph readers (226). However, it is not clear whether the paired radiographs (from baseline and follow-up) were read sequentially. Studies have shown that if the chronological order of the radiographs is known, there is an increase in both reproducibility and sensitivity of the readings (295). Further information regarding the order of reading radiographs in the Chingford Study is required.

Limitations with statistical analysis

The model was built using logistic regression, as there was no time to event data measured in Chingford. Hand radiographs were only taken at one follow up period, ten years from baseline. If hand radiographs had been taken more frequently, it might have been possible to assess the time point at which participants developed IPJ osteoarthritis. This would have allowed for a Cox model to be developed. It is possible that there might be different phenotypes of hand or IPJ osteoarthritis, in which one phenotype develops earlier than another. For example, erosive hand osteoarthritis may result in accelerated disease, and, if time to event data was available, it may be possible to separate out this phenotype and to compare whether prognostic factors for each are similar or different.

3.5.3 Strengths

This prediction model focussed on middle aged women, in whom the incidence of hand osteoarthritis is known to be highest, assessing the highest risk population (26). This is also the first model to assess incident radiographic IPJ osteoarthritis. The model performed better than previously published models for incident hand osteoarthritis (210, 211). The KL atlas, used to define IPJ osteoarthritis in this model, has also been shown to be highly replicable, with a high ICC for intra-reader and inter-reader reliabilities.

This prediction model included a large number of potential predictors for incident IPJ osteoarthritis. The use of elastic net penalization allowed the model to be penalised by shrinking the regression coefficients towards zero to minimise the risk of overfitting. This methodology is preferable to backwards selection, which has previously been used to develop prediction models for incident hand osteoarthritis (210, 211). Backwards selection could lead to the spurious removal of candidate predictors from a model if these predictors have small predictive roles for the outcome (296). This means the overall risk of the outcome due to a combination of predictors being present cannot be fully assessed.

3.5.3.1 Translating research to clinical practise

<u>Nomogram</u>

The model was developed into a clinically useful tool through a nomogram. Historically, clinicians might estimate risk through their own anecdotal experience or their memory of clinical encounters. This can be subjective, allowing for bias in making predictions (297). In particular there is concern that clinicians might be more likely to predict preferred outcomes, instead of the most mathematically accurate outcomes (298). If a large list of predictors is required, it is also difficult to take all of these into account (299, 300). To overcome these limitations, prediction tools such as nomograms, risk-grouping, look-up tables, tree analyses, and artificial neuronal networks have all been developed. Nomograms are considered to be more accurate than other types of predictive tools, particularly as they can include multiple predictors, and continuous variables (297). More recently, nomograms are being developed into online web calculators or applications.

The nomogram created for this model can only be used in middle-aged women, similar to those recruited to the Chingford Study. In clinical practice, if the nomogram is used, all of the predictors listed on the nomogram must be captured. This means that a clinician must have information on all of the predictors in the nomogram, in order to use it. Excluding any predictor could make decrease the predictive ability of the nomogram, and would need to be assessed by developing a new prediction model and testing its performance measures (discrimination and calibration). When using nomograms accurately, they have been shown to outperform predictions made by clinicians (300). The use of the nomogram from this study in comparison to predictions from clinicians needs to be assessed before it can be used clinically. Further work could also consider adjusting the nomogram for 'competing risks' (297), such as the change in risk of incident IPJ osteoarthritis if predictors are modified before the disease onset.

Decision Curve

At the risk threshold of 40%, the net benefit of using the model is higher compared to clinically assessing all patients. After this threshold, the net benefit is marginal compared to clinically assessing all patients.. After a 50% risk threshold, the prediction model can still be used, but the cost of using the model increases. This suggests that in patients who have a perceived 50% risk of developing IPJ osteoarthritis, it is not cost effective to use the model, and instead these patients could directly be referred to treatment or prevention pathways, if clinically appropriate.

The decision curve analysis was undertaken using data from the Chingford Study. This means a data driven approach was used to set the risk thresholds. The decision curve analysis could be improved by identifying whether there is a risk threshold used by clinicians, after which assessment of patients is no longer required, because the risk of incident IPJ osteoarthritis is so high, the patient can be managed appropriately (265, 267). This is particularly important if a disease is aggressive, and clinicians would accept a lower specificity but higher sensitivity (i.e.- more false positives but fewer false negatives) (268). Data on risk thresholds for assessment or management of IPJ osteoarthritis does not yet exist in the hand osteoarthritis literature. To overcome the lack of this data, the decision curve can be externally validated in another dataset. However, to date, there is no external dataset which contains similar candidate predictors to Chingford and future prospective longitudinal studies would benefit from harmonisation of data, to allow for external validation of studies.

The decision curve analysis also assumes there is a cost for misclassification of patients (false positive or false negative), but that there is no cost for correct classification (true positive or true negative) (268). Instead, it is likely that there is an associated cost for correct classification, such as radiation exposure from hand radiographs. Therefore, health economic data is required to better estimate the cost:benefit ratio used to analyse the data.

3.5.4 Future research

The prediction model was built in the Chingford Study. It could not be externally validated due to a lack of common variables (candidate predictors) between hand osteoarthritis datasets. External validation is required to ensure that the model works in a different population. If the model does not perform well, the model could be updated (re-calibration of the intercept) for the external population. Further work is required to externally validate this prognostic model. The decision curve analysis was also developed using a data driven approach from the Chingford Study. It also requires external validation in another dataset, clinical data to inform risk thresholds, and health economic data to inform cost:benefit analysis.

This prediction model focused on incident radiographic IPJ osteoarthritis. My systematic review showed plain film radiographs are most commonly used to diagnose osteoarthritis in prognostic factor studies (Chapter 2). Further work is needed to investigate whether the use of different imaging modalities, such as ultrasound or magnetic resonance imaging, could be used particularly for inflammatory and erosive phenotypes.

The importance of early, possible radiographic features, such as the possible presence of osteophytes or possible joint space narrowing, as potential risk factors for incident radiographic IPJ osteoarthritis at followup could also be investigated. In a prediction model for incident radiographic knee osteoarthritis (defined as KL ≥2 in at least one knee), KL grade 1 (compared to KL grade 0) at baseline was found to be an important risk factor (277). The prediction model which included KL grade 1 at baseline as a candidate predictor also had a higher discrimination than the prediction model without this candidate predictor, further highlighting its importance as a risk factor (277). Future prediction models for incident IPJ osteoarthritis could consider including KL grade 1 or other similar radiographic features at baseline as candidate predictors.

4 CHAPTER 4: PROGNOSTIC MODEL: PROGRESSION OF RADIOGRAPHIC IPJ OSTEOARTHRITIS

4.1 Chapter Aims

This chapter will investigate how the potential risk factors identified from the systematic review and Delphi study predict the progression of IPJ osteoarthritis, through prognostic modelling (Chapter 2). In this chapter, IPJ osteoarthritis always refers to the radiographic classification.

4.2 Introduction

Prognostic factors for the progression of IPJ osteoarthritis have been poorly characterised in the literature (Chapter 2). Few studies have investigated such factors, and results lack strong evidence. It is possible that 'novel' risk factors for IPJ osteoarthritis progression exist, but have not yet been investigated in the literature. Identifying these risk factors will add to the existing knowledge and provide a more robust understanding of which patients are at risk of their IPJ osteoarthritis deteriorating. The relationship between multiple risk factors and the overall effect on disease progression has also not yet been assessed, with a lack of phase 3 prognostic model research (143, 144, 301). Using cohort studies to develop prediction models will allow us to calculate the overall risk of IPJ osteoarthritis progression when multiple potential risk factors are present (142). In particular, population-based studies could enable us to identify these 'novel' risk factors, which have not yet been investigated.

Classifying the progression of IPJ osteoarthritis is also controversial, and no consensus has yet been established (Chapter 2). The progression of osteoarthritis can be used as an outcome measure in academic studies. The KL atlas (79) was used by all studies in the systematic review to measure the progression of IPJ osteoarthritis (Chapter 2). Progression was described as either osteoarthritis spread to additional IPJs, or worsening of disease at an IPJ with osteoarthritis, over time, most commonly measured on an ordinal scale for the number of IPJs with osteoarthritis progression. This suggests that either classification method could be used, with a continuous outcome measure.

4.2.1 Objective

The objective was to develop a prognostic model for the progression of IPJ osteoarthritis, using a prospective population-based cohort study.

4.3 Methodology

4.3.1 Reporting Guideline and Ethical approval

The reporting of these models follows the TRIPOD guideline (212). Ethical approval has been established for ongoing analysis of The Chingford 1000 Women Study (South Central- Oxford A Research Ethics Committee: REC reference 13/SC/0156). No further approval was required for this study. Institutional Review Board (IRB) approval for analysis of JoCo Project was gained from the University of North Carolina (IRB ID 251233).

4.3.2 Study design

A prognostic model (i.e.- a prediction model for the progression of disease) was developed (as described in Appendix 3.1).

4.3.3 Data Sources

Data from two-population based prospective cohort studies were used for the current study: the Chingford Study and JoCo Project.

The Chingford 1000 Women Study

Details for the Chingford Study have been previously described in section 3.3.4. This prediction model was developed in the Chingford Study, similar to the prediction model for incident IPJ osteoarthritis, which had also been developed in the Chingford Study (Chapter 3).

The Johnston County Osteoarthritis Project

The JoCo Project was developed to study ethnic differences in hip and knee osteoarthritis. Based in North Carolina, residents over the age of 45 years were recruited from six townships in Johnston County (302). There was also subsampling of Caucasian women over the age of 65 years. Hand radiographs were not taken at baseline, but were taken at the first follow-up between 1999 and 2003 (known as T1), the second follow-up between 2006 and 2011 (known as T2), and between 2013 and 2015 (known as T3). All hand radiographs have been read paired and in known time order, by one musculoskeletal (MSK) radiologist (JBR) using the KL atlas (79). Intra-observer kappa values between 0.72 and 0.86 have been reported for T1 and T2 (not available for T3) (303). For the current study, radiographs and participant characteristics taken at T1 were considered as 'baseline', and radiographs taken at T3 were considered as 'follow-up'. Radiographs at T2 were not considered due to the amount of missing data (66 (7.4%) of participants), and the shorter time interval between T1 and T2, compared to baseline and follow-up in the Chingford Study. The prediction model was externally validated in the JoCo Project, to test its transportability. Transportability assesses model performance across a different but plausibly related population (231, 261, 263, 304).

4.3.4 Study participants

Participants with radiographs at baseline which showed radiographic osteoarthritis (KL ≥2 in ≥1 IPJ) were eligible for the current study. Exclusion criteria were participants without radiographs at baseline and follow-up, participants with unreadable radiographs at baseline or follow-up (for example, all of the fingers were not captured), participants with no osteoarthritis at baseline, participants with KL 4 in all IPJs at baseline (i.e.- no potential for osteoarthritis progression), and participants with random error of radiographic reading (for example, a decrease in KL score at follow-up compared to baseline). From the JoCo Project, any male or non-Caucasian participants were also excluded.

4.3.5 Outcome

Osteoarthritis progression was defined as an increase of ≥1 KL grade in ≥1 IPJ at follow up compared to baseline (with the exception of KL grade 0 to 1, which was not counted as progression), in both the Chingford Study and the JoCo Project. The KL atlas was chosen as both the Chingford Study and the JoCo Project included hand radiographs which had already been read using the KL atlas. This corroborated with results from the systematic review, which found that all studies published in the literature classified IPJ osteoarthritis using the KL atlas (Chapter 2). In the Chingford Study, follow-up radiographs were taken after ten years, whilst in the JoCo Project follow-up radiographs were taken after 12 to 14 years. No erosive IPJ osteoarthritis was identified in the Chingford Study or the JoCo Project. There was no time to event data, as hand radiographs were not taken at multiple time intervals, and therefore a survival or Cox model could not be used.

The outcome was measured on an ordinal scale for the number of IPJs with progression of osteoarthritis. The frequency and the probability density for the number of participants per number of IPJs with progression of osteoarthritis was assessed using a histogram and a Kernel Density plot in the Chingford Study (Appendix 4.1). These showed peaks at three to five IPJs, and therefore the outcome was truncated at ≥6 IPJs with osteoarthritis progression at follow-up for both the Chingford Study and the JoCo Project. The outcome categories were:

- 0 IPJs with osteoarthritis progression
- 1 IPJ with osteoarthritis progression
- 2 IPJs with osteoarthritis progression

- 3 IPJs with osteoarthritis progression
- 4 IPJs with osteoarthritis progression
- 5 IPJs with osteoarthritis progression
- ≥6 IPJs with osteoarthritis progression.

Sensitivity analysis

As the outcome definition was broad, and the systematic review (Chapter 2) identified that the progression of IPJ osteoarthritis could be considered as either spread to additional IPJs, or worsening of osteoarthritis at an IPJ which is already affected, sensitivity analyses were performed in the Chingford Study:

a) Geographical progression

Geographical progression was defined as osteoarthritis (KL ≥2) spread at follow-up to IPJs which did not have osteoarthritis at baseline. This was measured on an ordinal scale for the number of IPJs with geographical osteoarthritis progression. Participants with osteoarthritis (KL ≥2) in all IPJs at baseline were excluded, as progression to other IPJs at follow-up was not possible.

b) Local progression

Local progression was defined as worsening osteoarthritis (an increase by KL ≥1) at follow-up in an IPJ with osteoarthritis (KL ≥2) at baseline (i.e.- from KL 2 at baseline to KL 3 or 4 at follow-up, or from KL 3 at baseline to KL 4 at follow-up). This was measured on an ordinal scale for the number of IPJs with local osteoarthritis progression. Participants with KL 4 in the IPJs with osteoarthritis at baseline were excluded, as it was not possible for osteoarthritis to progress in those IPJs.

4.3.6 Candidate predictors

There is currently no guidance of sample size for developing prognostic models with ordinal outcomes, and thus, to decrease the risk of overfitting the model to the data (fitting the model to random noise), the number of candidate predictors was minimised (263). Candidate predictors were chosen based on possible biological plausibility, results from the systematic review and Delphi study (Chapter 2), and results from the prediction model for the incidence of IPJ osteoarthritis (Chapter 3). Five candidate predictors were included in the model. The methods of data capture for each candidate predictor, and how the data was manipulated for the current study, are described in Appendix 4.2.

1. Age (years)
2. BMI (kg/m^2)
3. Occupation (manual versus non-manual)
4. History of radiographic first CMCJ osteoarthritis (KL ≥2 (yes), versus KL <2 (no))
5. History of hand osteoarthritis in family (yes versus no)

<u>Outliers</u>

Continuous candidate predictors (age and BMI) were investigated for outliers using boxplots (methodology detailed in section 3.3.7). Outliers which were not biologically plausible were coded as missing data.

<u>Linearity with the outcome</u>

Continuous candidate predictors were investigated for linearity with the outcome. A partial residual plot was developed, a plot of the predictor values against its partial residuals (smoothed using locally weighted scatterplot smoothing line), to examine whether the shape and slopes of all the curves (for each category) were 'similar' (305, 306). Splines (RCS) were also used to assess the relationship between each predictor and each outcome category (Appendix 4.3). As these appeared unstable, the linear forms for both age and BMI were used in the model.

4.3.7 Statistical analysis

All analyses were performed in R statistical software version 4.0.2, using the following packages (234): for data cleaning, coding and manipulation: plyr (235), dplyr (236), tidyr (237), DescTools (238); for data visualisation: ggplot2 (239), MASS (240); for assessing missingness: naniar (242), VIM (243); for building the model and assessing model performance: Hmisc (246), rms (247).

All analyses were performed at the person level. Due to the model being on a six-level ordinal scale, a proportional odds (ordinal) logistic regression model was fitted (307). In a proportional odds model, the assumption is that for each term in the model, the estimate (slope) between each pair of outcomes is the same; only the intercept changes. Therefore, one effect measure is reported for each predictor across all outcome categories. The proportional odds assumption was tested in multiple ways, as there is no single 'gold-standard' test. This assumption was tested by graphically stratifying the means of the predictors by the levels of the outcome (305). Across each predictor, the ordinal outcome categories should show either an increasing or decreasing pattern, for the assumption to be satisfied (304, 305). The assumption was also tested by visualising the logits for all levels of the outcome for each level of the predictors. The outcome should show a similar distance between the logits of the outcome for each level of the predictor for the assumption to be satisfied (304, 305).

To prevent overfitting of the model to the data, penalised maximum likelihood estimation (PMLE) was used. PMLE is recommended for proportional odds models as it has the lowest variance (305). A PMLE applies a penalty factor (λ) to each regression coefficient (306). The penalty factor shrinks the regression coefficient towards zero, to adjust for the model being too closely fitted to the dataset. The penalty factor is chosen by trial and error method of multiple penalty factors, to select the one with the largest AIC (306).

Internal validation

The model was internally validated using 2,000 bootstrap iterations. Bootstrapping is a method of internal validation, used to adjust for the optimism in models (the apparent predictive performance of a model, which is usually higher than the actual performance, as it is calculated in the derivation dataset) (212). The description of bootstrapping methodology is detailed in Chapter 3 (section 3.3.8, under Sensitivity analysis). For each predictor, an OR with 95% CI was reported after internal validation.

Model performance

Model performance was assessed through discrimination (C-statistic) (254) and calibration (258) (calibration slope, and visualised by calibration plots for each outcome level). Descriptions of what they are, how to interpret them are detailed in Chapter 3 (section 3.3.8). Optimism corrected performance measures are reported (212).

External validation

The model was externally validated in the JoCo Project. The model's performance was assessed in the JoCo Project by assessing discrimination and calibration. If mis-calibration was identified, the model was re-calibrated in the JoCo Project by updating the coefficients of the intercepts (262, 270, 271) (as detailed in section 3.3.8, under Sensitivity analysis).

Sensitivity analysis

Sensitivity analyses was performed for geographical and local progression in the Chingford Study. Participants with both geographical and local progression were excluded from the sensitivity analysis, to prevent the effect of one subgroup on the other. The model's performance was assessed in each subgroup by analysing discrimination and calibration. If mis-calibration was identified, the model was re-calibrated by updating the coefficients of the intercepts (270, 271).

Missing data

Missing data was examined for patterns of missingness in the Chingford Study and the JoCo Project (as detailed in section 3.3.8, under Sensitivity analysis). If ≤5% of data was missing and it was considered to be MAR or MCAR, a 'complete case analysis' was used (272, 273). If >5% of data was missing, MICE was planned (as detailed in section 3.3.8, under Missing data).

In the Chingford Study, seven participants (3.4%) were missing data: occupation (four participants), BMI (one participant), family history of hand osteoarthritis (one participant), and both occupation and history of hand osteoarthritis (one participant). No patterns of missingness were found (Appendix 4.4), and missing data was assumed to be MCAR. Complete case analysis was used.

In the JoCo Project, six participants (3.8%**)** were missing data (occupation: five participants), family history of osteoarthritis (one participant) (Appendix 4.5), and missing data was assumed to be MCAR. Complete case analysis was carried out, whereby data on individuals for which there was complete information on all candidate predictors and outcome was used.

4.4 Results

4.4.1 Study participants

The Chingford 1000 Women Study

There were 1,003 participants in the Chingford Study, of which 304 (30.3%) did not have radiographs and 34 (3.4%) did not have readable radiographs. Of 665 participants with readable radiographs, 459 (69.0%) did not have osteoarthritis at baseline. Participants without radiographs at baseline, with radiographs but without osteoarthritis at baseline, and with radiographs and with osteoarthritis at baseline (included in this study) were compared (Chapter 3). Participants with osteoarthritis at baseline were older, more likely to have first CMCJ osteoarthritis, and more likely to have a family history of hand osteoarthritis (Table 3.1).

Of 206 participants with osteoarthritis at baseline, 4 (1.9%) had a reading error. Using complete case analysis, 195 participants were included in the study with 181 (92.8%) having osteoarthritis progression (an increase of ≥1 KL grade in ≥1 IPJ at follow up compared to baseline) (Figure 4.1) At baseline, median age was 59.0 (IQR: 8.0) years, with median BMI of 26.7 (IQR: 4.8) kg/m^2 (Table 4.1).

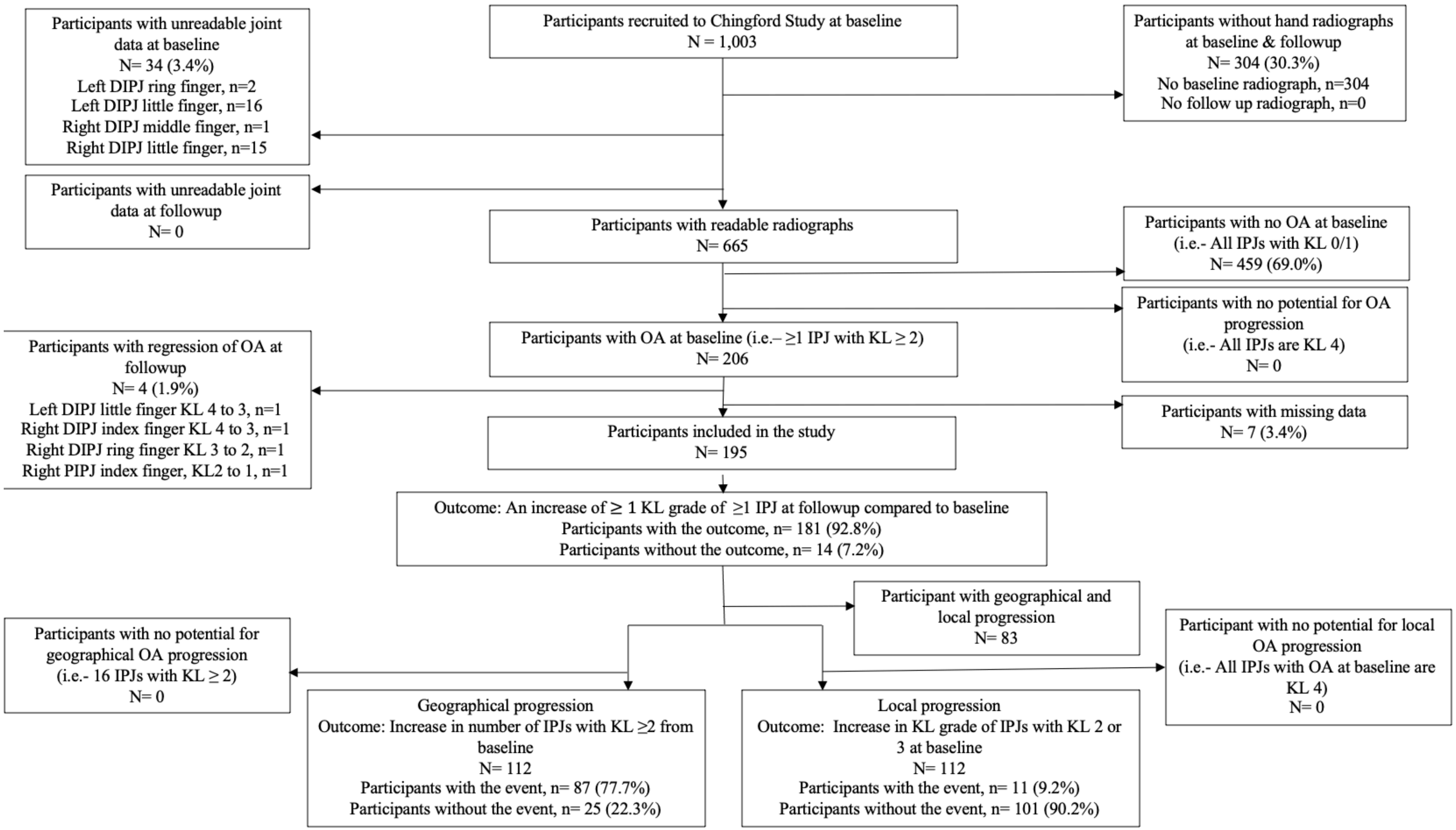


Figure 4.1: Flowchart of participants included from The Chingford 1000 Women Study

IPJ: Interphalangeal joint; KL: Kellgren Lawrence; OA: Osteoarthritis

Table 4.1: Baseline demographics of participants included from The Chingford 1000 Women Study

Predictor	Number of participants by number of IPJs with progression							All participants N= 195
	0 n= 14	1 n= 33	2 n= 20	3 n= 21	4 n= 26	5 n= 18	≥6 n= 63	
Age (years) [median (IQR)]	59.5 (9.5)	57.0 (8.0)	56.5 (7.8)	61.0 (7.0)	62.0 (9.5)	59.0 (6.5)	59.0 (7.0)	59.0 (8.0)
BMI (kg/m^2) [median (IQR)]	27.4 (5.1)	26.3 (4.4)	25.3 (3.9)	25.1 (4.5)	26.8 (3.4)	27.3 (5.9)	27.8 (4.8)	26.7 (4.8)
Occupation [n (%)]								
Non-manual	12 (86)	22 (64)	16 (80)	18 (86)	20 (77)	16 (89)	51 (81)	154 (79)
Manual	2 (14)	12 (36)	4 (20)	3 (14)	6 (23)	2 (11)	12 (19)	41 (21)
OA at first CMCJ [n (%)]								
No	4 (29)	9 (27)	4 (40)	9 (43)	15 (68)	12 (67)	31 (49)	107 (55)
Yes	10 (71)	24 (73)	12 (60)	12 (57)	11 (42)	6 (33)	32 (51)	88 (45)
Family history of hand OA [n (%)]								
No	6 (43)	13 (39)	10 (50)	11 (52)	12 (46)	7 (39)	29 (46)	107 (55)
Yes	8 (57)	20 (61)	10 (50)	10 (48)	14 (54)	11 (61)	34 (54)	88 (45)

BMI: Body mass index; CMCJ: Carpometacarpal joint; IPJ: Interphalangeal joints; IQR: Interquartile range; OA: Osteoarthritis
Osteoarthritis progression was defined as an increase of ≥1 KL grade in ≥1 IPJ at follow up compared to baseline

The Johnston County Osteoarthritis Project

There were 892 participants in the JoCo Project, of which 66 (7.4%) did not have radiographs and 8 (0.1%) did not have readable radiographs. Of 818 participants with readable radiographs, 559 (68.3%) did not have osteoarthritis at baseline. Participants with and without IPJ osteoarthritis at baseline (included in this study) were compared (Table 4.2). The proportion of participants without radiographs at baseline was low and therefore no comparisons were made. Participants with osteoarthritis at baseline were older, more likely to be female, Caucasian, and work in non-manual occupations, compared to those without osteoarthritis at baseline. The prevalence of first CMCJ osteoarthritis was higher in those with IPJ osteoarthritis at baseline compared to those without (Table 4.2)

Of 259 participants with osteoarthritis at baseline, 68 (26.3%) were male and 35 (13.5%) were non-Caucasian, and were excluded. When data on participants for which there was complete information on all candidate and predictors and outcomes was used (i.e.- complete case analysis), 150 participants were included in the study with 140 (93.3%) having osteoarthritis progression (an increase of ≥1 KL grade in ≥1 IPJ at follow up compared to baseline) (Figure 4.2).

At baseline, median age in the JoCo Project was 63.8 (IQR: 10.0) years, which was higher than in the Chingford Study (Table 4.3). The prevalence of manual occupation was also higher in the JoCo Project (27%) compared to the Chingford Study (21%), and similarly the prevalence of a family history of osteoarthritis was higher in the JoCo Project (88%) compared to the Chingford Study (55%). In the JoCo Project the prevalence of first CMCJ osteoarthritis was lower (33%) compared to the Chingford Study (55%).

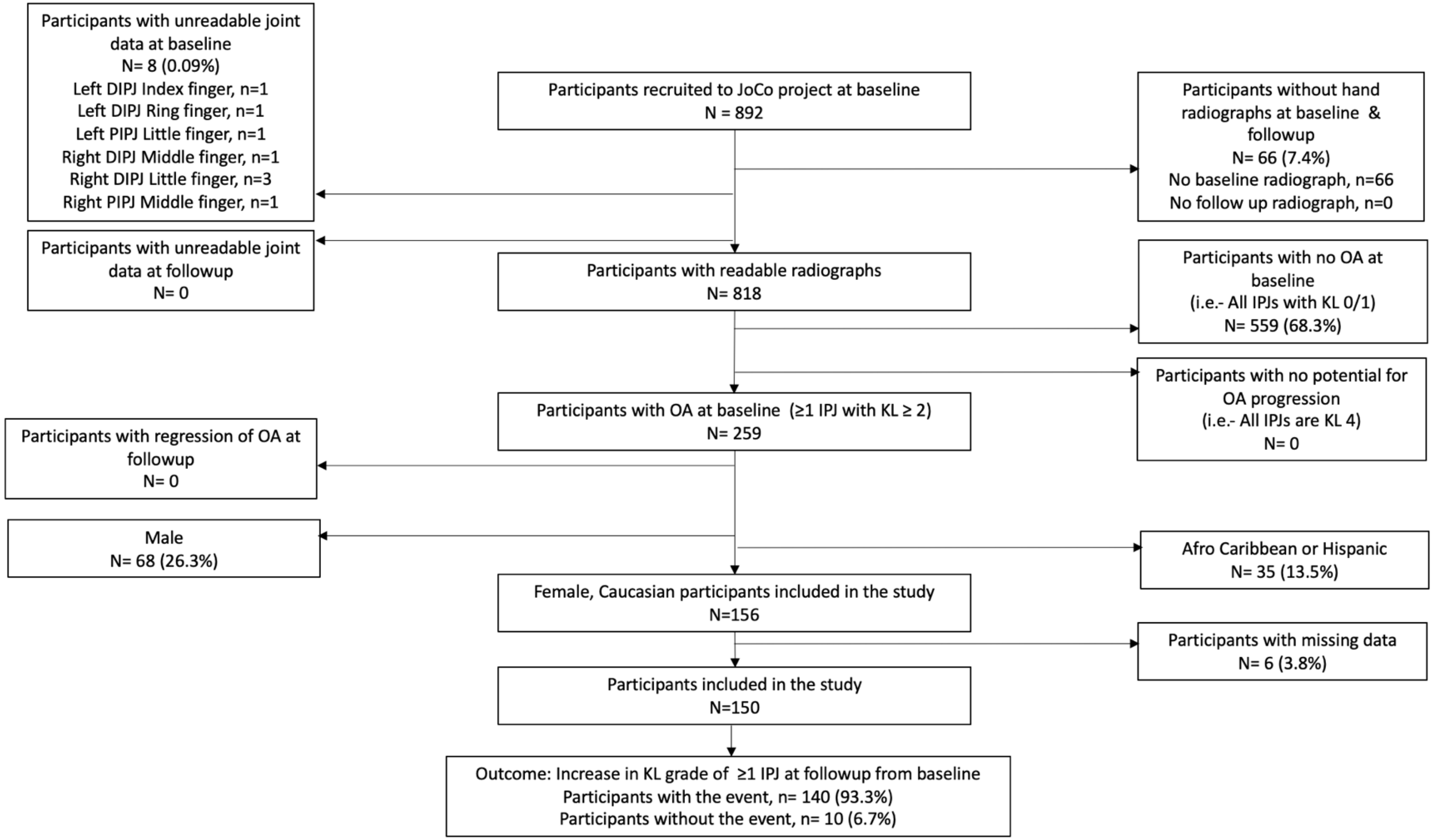


Figure 4.2: Flowchart of participants included from The Johnston County Osteoarthritis Project

IPJ: Interphalangeal joint; KL: Kellgren Lawrence; OA: Osteoarthritis

Table 4.2: Demographics of participants with and without IPJ osteoarthritis at baseline in The Johnston County Osteoarthritis Project

Demographic	Participants with no OA at baseline: N= 559	Participants with OA at baseline N= 259
Age (years) [median (IQR)]	57.0 (9.8)	64. 2 (11.7)
Sex [n (%)]		
Male	196 (35)	68 (26)
Female	363 (65)	191 (74)
Missing data	0	0
Race [n (%)]		
Caucasian	342 (61)	216 (83)
Afro-Caribbean/ Hispanic	217 (39)	43 (17)
Missing data	0	0
BMI (kg/m^2) [median (IQR)]	30.3 (8.1)	28.9 (6.7)
Occupation [n (%)]		
Non-manual	277 (50)	158 (61)
Manual	258 (46)	93 (36)
Missing data	24 (4)	8 (3)
OA at first CMCJ [n (%)]		
No	514 (92)	185 (71)
Yes	43 (8)	72 (28)
Missing data	2 (0)	2 (1)
Family history of any OA [n (%)]		
No	103 (18)	49 (19)
Yes	447 (80)	207 (80)
Missing data	9 (2)	3 (1)

BMI: Body mass index; CMCJ: Carpometacarpal joint; IQR: Interquartile range; OA: Osteoarthritis

Table 4.3: Demographics of participants included from The Chingford 1000 Women Study and The Johnston County Osteoarthritis Project at baseline

Demographic	Chingford Study N= 195	JoCo Project N= 150
Age (years) [median (IQR)]	59.0 (8.0)	63.8 (10.0)
BMI (kg/m^2) [median (IQR)]	26.7 (4.8)	28.6 (7.7)
Occupation [n (%)]		
Non-manual	154 (79)	109 (73)
Manual	41 (21)	41 (27)
OA at first CMCJ [n (%)]		
No	88 (45)	100 (67)
Yes	107 (55)	50 (33)
Family history of OA [n (%)]		
No	88 (45)	18 (12)
Yes	107 (55)	132 (88)

BMI: Body mass index; Chingford: The Chingford 1000 Women Study; CMCJ: Carpometacarpal joint; IQR: Interquartile range; JoCo Project: Johnston County Osteoarthritis Project; OA: Osteoarthritis
Osteoarthritis progression was defined as an increase of ≥1 KL grade in ≥1 IPJ at follow up compared to baseline

4.4.2 Candidate predictors

The median age and the median BMI were similar between participants without IPJ osteoarthritis progression at follow-up, and across those with different numbers of IPJs with osteoarthritis progression (Table 4.1). The proportion of patients who worked in manual occupation, the proportion of patients with first CMCJ radiographic osteoarthritis at baseline, and the proportion of participants with a family history of hand osteoarthritis all peaked in participants whom had one IPJ with osteoarthritis progression at follow-up (Table 4.1).

4.4.3 The model

The assumption of proportional odds held for all predictors when stratifying the means of the predictors by the levels of the outcome, with all showing an increasing order, except for occupation which showed a decreasing order (Appendix 4.6). However, when visualising the logits for all levels of the outcome for each level of the predictors, the assumption did not appear to hold (Appendix 4.6).

The final model (after penalization and internal validation) found no predictors to be statistically significantly associated with the progression of IPJ osteoarthritis (Table 4.4). First CMCJ osteoarthritis was the strongest predictor for IPJ osteoarthritis progression, though was not significant. For the presence of first CMCJ osteoarthritis in at least one joint compared to no joints, the odds of IPJ osteoarthritis progression in n IPJs compared to <n IPJs was 1.32 (95% CI: 0.93 to 1.88).

<u>Optimism corrected model performance:</u>

The optimism corrected discrimination of the model was poor (C-statistic: 0.57), and the model was mis-calibrated (calibration slope for the middle outcome level (≥3 IPJs with osteoarthritis progression): 1.38) The calibration plots show for all outcome levels the calibration of the model was poor (Figure 4.3). For the middle outcome level, at lower levels of predicted IPJ osteoarthritis progression, the observed progression was lower, whilst at higher levels of predicted IPJ osteoarthritis progression, the observed progression was higher (308) (Figure 4.3).

Table 4.4: Coefficients, Odds ratios and 95% confidence intervals for the prognostic model for the progression of IPJ osteoarthritis

Predictor	Odds ratio (95% confidence interval)	Regression coefficient
Age (years)	1.02 (0.99 to 1.06)	0.03
BMI (kg/m^2)	1.04 (0.99 to 1.09)	0.04
Occupation (manual versus non manual)	0.88 (0.60 to 1.29)	-0.13
OA at first CMCJ (yes versus no)	1.32 (0.93 to 1.88)	0.28
Family history of OA (yes versus no)	1.03 (0.72 to 1.45)	0.03
Intercept		
≥1 IPJs	-	0.09
≥2 IPJs	-	-0.34
≥3 IPJs	-	-1.86
≥4 IPJs	-	-2.33
≥5 IPJs	-	-2.89
≥6 IPJs	-	-3.29

BMI: Body mass index; CMCJ: Carpometacarpal joint; IPJ: Interphalangeal joints; OA: Osteoarthritis
Osteoarthritis progression was defined as an increase of ≥1 KL grade in ≥1 IPJ at follow up compared to baseline

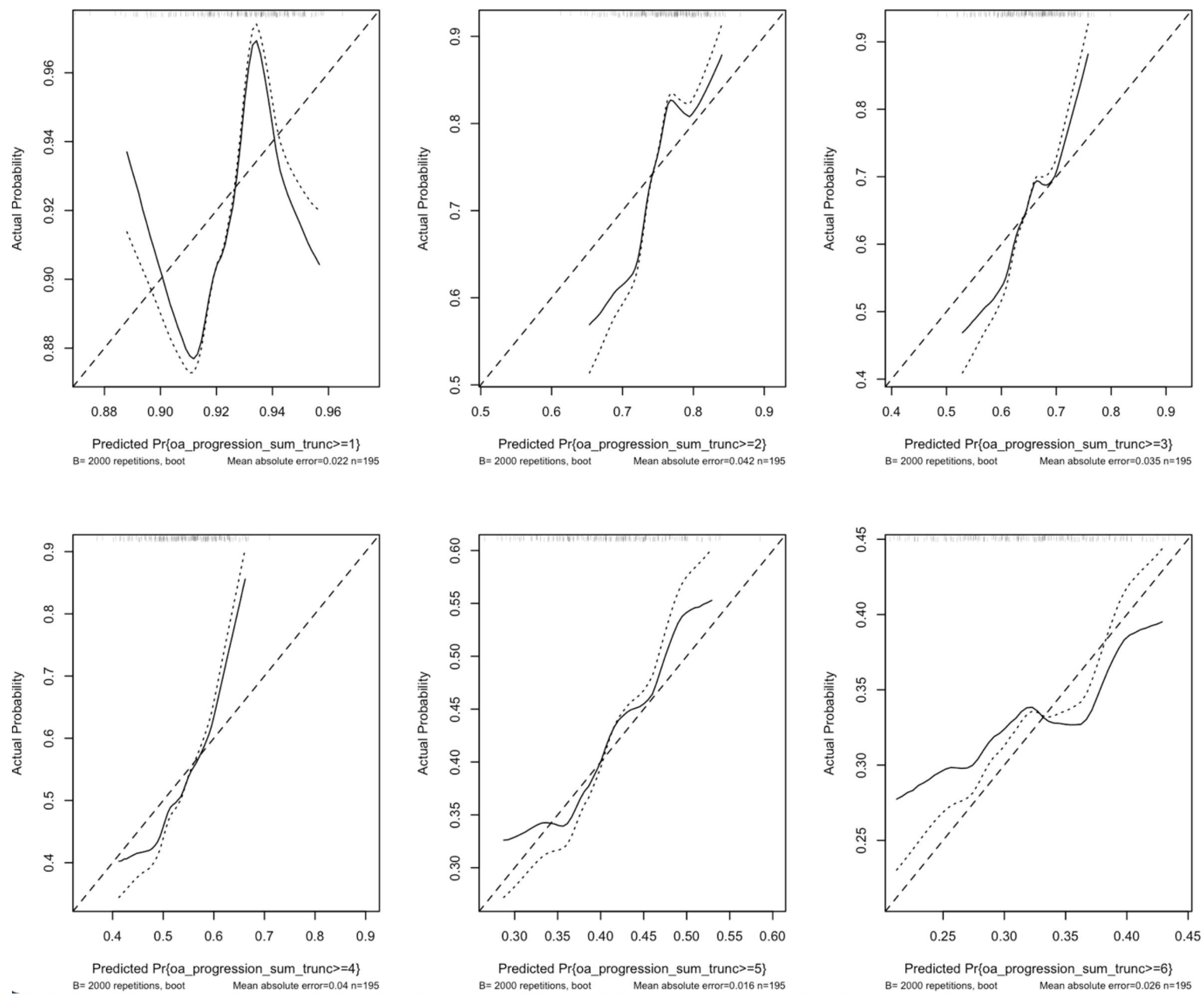


Figure 4.3: Calibration plots for each level of the outcome of the prognostic model

Number of IPJs with osteoarthritis progression (from top left to bottom right): a) ≥1 IPJs, b) ≥2 IPJs, c) ≥3 IPJs, d) ≥4 IPJs, e) ≥5 IPJs, f) ≥6 IPJs

X axis: Predicted probability from the model
Y axis: Actual probability from the dataset
The dashed line (45° angle) represents perfect calibration.
The dotted line represents calibration of the model before correcting for overfitting.
The continuous line represents calibration of the model after correcting for overfitting through penalised maximum likelihood estimation and 2,000 bootstrap iterations.

External validation of the model

When the calibration of the original model was evaluated in the JoCo Project, it was poor. The model was re-calibrated in the JoCo Project, but it remained poor (Figure 4.4). When discrimination of the original model was externally validated in the JoCo Project, it improved to 0.59.

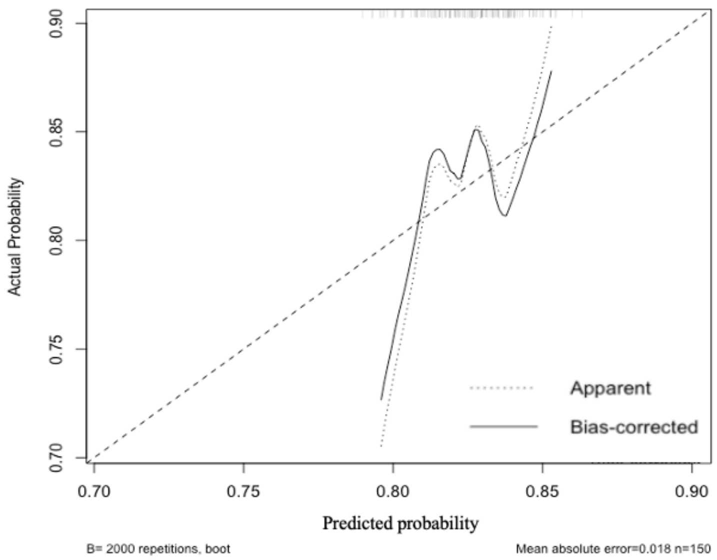


Figure 4.4: Calibration plot for re-calibrated model in The Johnston County Osteoarthritis Project for the middle outcome level (≥3 IPJs with osteoarthritis progression)

X axis: Predicted probability from the re-calibrated model
Y axis: Actual probability from the Johnston County Osteoarthritis Project
The dashed line (45° angle) represents perfect calibration.
The dotted line represents calibration of the re-calibrated model before correcting for overfitting.
The continuous line represents calibration of the re-calibrated model after correcting for overfitting through 2,000 bootstrap iterations

Sensitivity analyses

a) Geographical progression

From 195 participants in the dataset, 83 had both geographical and local progression and were excluded. There were no participants who had osteoarthritis in all IPJs at baseline. Therefore, 112 participants were included in the sensitivity analysis (Figure 4.1). Of these, 87 (77.7%) participants had geographical progression at follow-up (Figure 4.1). When the model was evaluated to assess whether it was able to predict geographical progression, it was mis-calibrated across the different outcome levels. The model was re-calibrated through updating the intercept of the original model (correction factor: -0.15) and the calibration slope showed improvement (Figure 4.5 shows the calibration plot for the middle outcome level).

b) Local progression

From 195 participants in the dataset, 83 had both geographical and local progression and were excluded. There were no participants who had KL grade 4 in all IPJs with osteoarthritis at baseline. Therefore, 112 participants were included in the sensitivity analysis (Figure 4.1). Of these, 11 (9.2%) participants had local progression at follow-up (Figure 4.1). As few participants had local progression, the model could not be assessed in this subgroup.

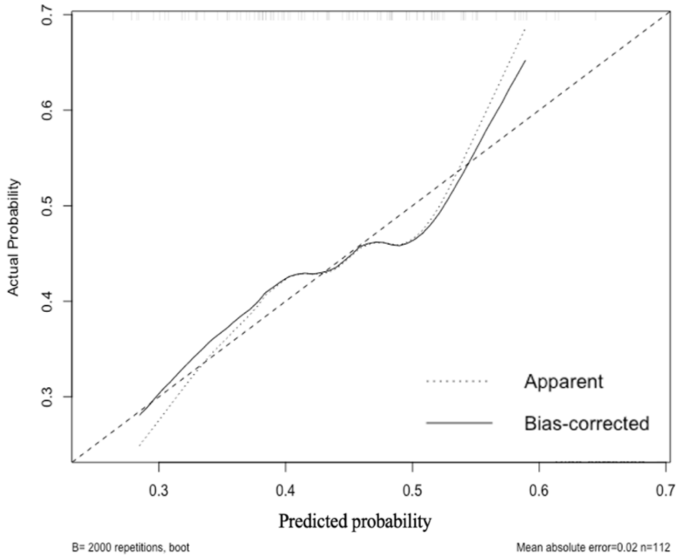


Figure 4.5: Calibration plot for re-calibrated model in subgroup for geographical progression for the middle outcome level (≥3 IPJs with osteoarthritis progression)

X axis: Predicted probability from the re-calibrated model
Y axis: Actual probability from geographical subgroup
The dashed line (45° angle) represents perfect calibration.
The dotted line represents calibration of the re-calibrated model before correcting for overfitting.
The continuous line represents calibration of the re-calibrated model after correcting for overfitting through 2,000 bootstrap iterations

4.5 Revising the model

The prognostic model showed poor performance, and when the model was externally validated and re-calibrated in the JoCo Project, despite the discrimination slightly improving, the model was not well calibrated. The participants in the JoCo Project were older, more likely to work in manual occupation, and less likely to have first CMCJ osteoarthritis, compared to the Chingford Study. Data was also captured differently across the cohorts. In particular, the JoCo Project captured data relating to a family history of osteoarthritis in all joints, whilst in the Chingford Study this was only focussed on a history of hand osteoarthritis. These differences between the cohorts is likely to have accounted for the low transportability of the model, and resulted in the poor calibration of the model in the JoCo Project.

The next logical step would be to revise the model in the external dataset, in an attempt to build a model with better performance. The calibration plot which showed poor calibration when transportability of the model was examined in the JoCo Project suggests there could be other predictors which have not been included in the model (261). These potential predictors might act on the estimated regression intercept and coefficients to cause poor calibration (262), and in particular, underfitting of the data (263). Participants included in the Chingford Study were all Caucasian women. However, the JoCo Project includes men and non-Caucasian participants. Therefore, the model was revised in the JoCo Project in both men and women, and including participants of all races, as additional candidate predictors.

4.5.1 Methodology

<u>Study participants</u>

The study participants were selected as previously described (section 4.3.4), with the exception that males and non-Caucasian participants were not excluded.

Outcome

The outcome was defined as an increase of ≥1 KL grade in ≥1 IPJ (although KL grade 0 to 1 was not considered to be osteoarthritis progression) at follow up (between 12 to 14 years) compared to baseline (as defined in section 4.3.5). The histogram and Kernel Density plot assessing the frequency and probability of the number of participants per number of IPJs with progression of osteoarthritis showed peaks at higher numbers (three to eight IPJs) (Appendix 4.7) than compared to the Chingford Study (three to five IPJs) (Appendix 4.8). Therefore, the outcome was truncated at ≥9 IPJs with osteoarthritis progression.

Candidate predictors

The candidate predictors were selected as previously described (section 4.3.6), with the addition of sex (female versus male) and race (non-Caucasian versus Caucasian). Age and BMI were assessed for linearity with the outcome, and for both they were found to be linearly associated with the outcome.

Sensitivity analysis

Both the geographical and local subgroups were assessed, as previously described (section 4.3.5 and 4.3.7).

Statistical analysis

The statistical analysis was performed as previously described (section 4.3.7). No further dataset exists to allow external validation of the revised model.

Missing data

Missing data was to be handled as previously described (4.3.7). From the data used to update the model, 13 (5%) participants had missing data: occupation (eight participants), family history of hand osteoarthritis (three participants), and history of hand osteoarthritis (two participants). No patterns of missingness were found (Appendix 4.9), and missing data was assumed to be MCAR. Data was used on participants with complete data on candidate predictors and outcome.

4.5.2 Results

Study participants

246 participants were included in the study to revise the model, with 230 (93.5%) having osteoarthritis progression (an increase of ≥1 KL grade in ≥1 IPJ at follow up compared to baseline) (Figure 4.6). A comparison between those with and without IPJ osteoarthritis has already been described (Table 4.2). At baseline, median age was 64.2 (IQR: 11.5) years, with median BMI of 29.1 (IQR: 6.9) kg/m^2, 74% of participants were female and 83% were Caucasian (Table 4.5).

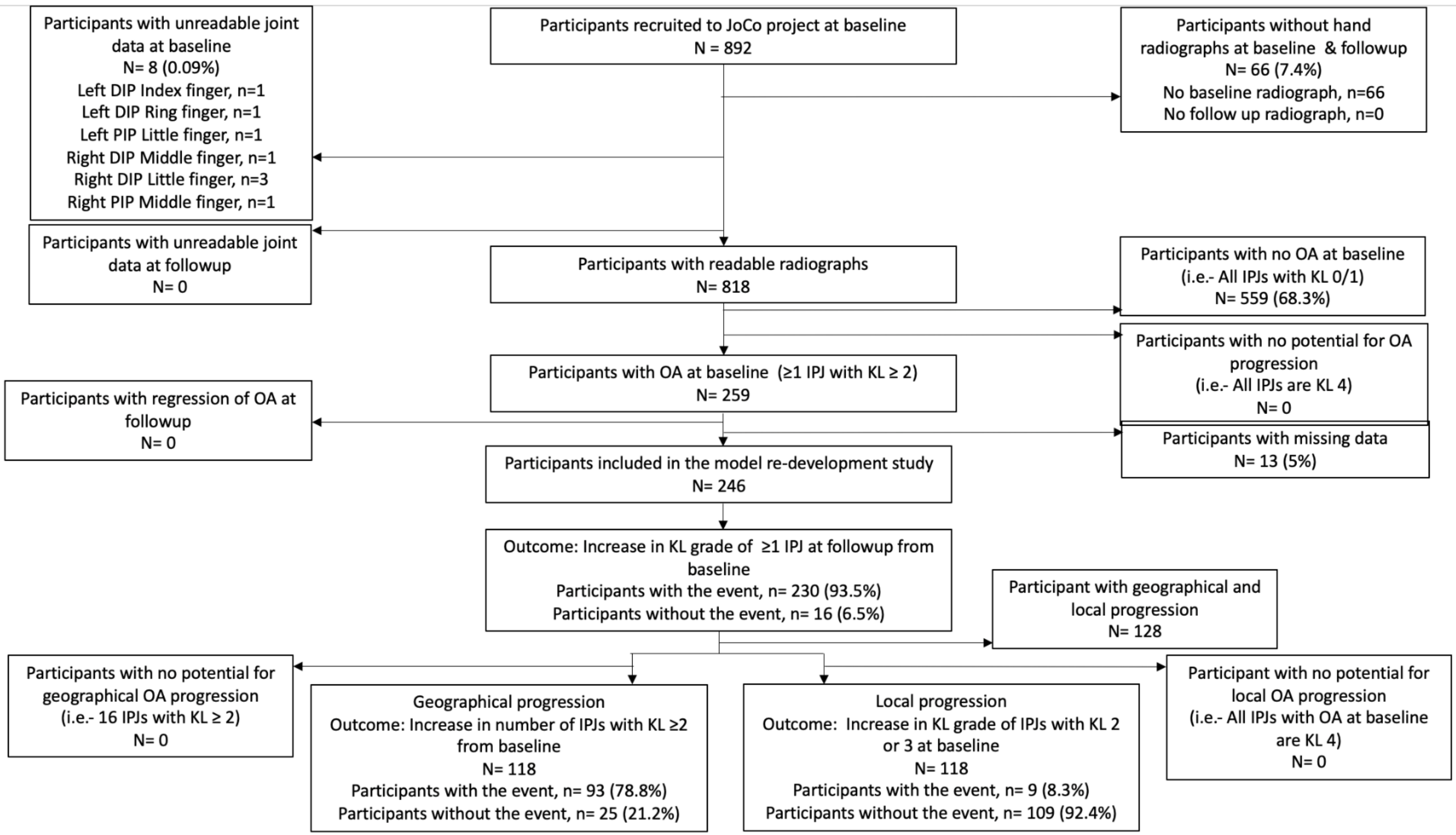


Figure 4.6: Flowchart of participants included in the revised model from The Johnston County Osteoarthritis project

IPJ: Interphalangeal joint; KL: Kellgren Lawrence; OA: Osteoarthritis

Table 4.5: Baseline demographics of participants included in the revised model from The Johnston County Osteoarthritis Project

Predictor	Outcome: Number of participants by number IPJs with progression										All participants N= 246
	0	1	2	3	4	5	6	7	8	≥9	
Age (years) [median (IQR)]	60.1 (14.0)	65.1 (8.7)	62.7 (10.9)	64.7 (11.1)	64,4 (6.7)	61.8 (11.0)	67.7 (11.3)	65.6 (10.5)	62.4 (12.3)	63.5 (12.1)	64.2 (11.5)
Sex [n (%)]											
Male	3 (19)	11 (50)	10 (48)	6 (32)	5 (25)	6 (27)	2 (11)	4 (19)	6 (23)	10 (17)	63 (26)
Female	13 (81)	11 (50)	11 (52)	13 (68)	15 (75)	16 (73)	17 (89)	17 (81)	20 (77)	50 (83)	183 (74)
Race [n (%)]											
Caucasian	11 (69)	17 (77)	14 (67)	18 (95)	18 (90)	19 (86)	14 (74)	18 (86)	21 (81)	55 (92)	205 (83)
Non-Caucasian	5 (31)	5 (23)	7 (33)	1 (5)	2 (10)	3 (14)	5 (26)	3 (14)	5 (19)	5 (8)	41 (17)
BMI (kg/m^2) [median (IQR)]	29.2 (5.5)	28.4 (5.6)	30.6 (9.3)	29.8 (6.9)	29.0 (6.6)	27.2 (6.8)	28.1 (11.4)	31.0 (5.0)	27.8 (5.7)	29.2 (6.4)	29.1 (6.9)
Manual occupation [n (%)]											
Non-manual	8 (50)	10 (45)	12 (57)	11 (58)	12 (60)	17 (77)	12 (63)	11 (52)	16 (62)	46 (77)	155 (63)
Manual	8 (50)	12 (55)	9 (43)	8 (42)	8 (40)	5 (23)	7 (37)	10 (48)	10 (38)	14 (23)	91 (37)
OA at first CMCJ [n (%)]											
No	14 (88)	18 (82)	19 (90)	13 (68)	13 (65)	14 (64)	13 (68)	13 (62)	20 (77)	41 (68)	178 (72)
Yes	2 (12)	4 (18)	2 (10)	6 (32)	7 (35)	8 (36)	6 (32)	8 (38)	6 (23)	19 (32)	68 (28)
Family history of OA [n (%)]											
No	5 (31)	7 (32)	5 (24)	2 (11)	4 (20)	3 (14)	5 (26)	5 (24)	5 (19)	7 (12)	48 (20)
Yes	11 (69)	15 (68)	16 (76)	17 (89)	16 (80)	19 (86)	14 (74)	16 (76)	21 (81)	53 (88)	198 (80)

BMI: Body mass index; CMCJ: Carpometacarpal joint; IPJ: Interphalangeal joints; IQR: Interquartile range; OA: Osteoarthritis
Osteoarthritis progression was defined as an increase of ≥1 KL grade in ≥1 IPJ at follow up compared to baseline

The revised model

The assumption of proportional odds held for all but two predictors (age and BMI) when stratifying the means of the predictors by the levels of the outcome (Appendix 4.6).

The final model (after penalization and internal validation) found female sex (versus male sex) was significantly associated with the progression of IPJ osteoarthritis (Table 4.6). For female gender compared to male sex, the odds of IPJ osteoarthritis progression in n IPJs compared to <n IPJs was 1.54 (95% CI: 1.03 to 2.32).

The discrimination of the model was poor (C-statistic: 0.57), and the model was mis-calibrated (calibration slope for the middle outcome level (≥5 IPJs with osteoarthritis progression): 1.18). For the middle outcome level, when the predicted probability of IPJ osteoarthritis progression was less than 0.52, the actual probability of progression was much lower (308) (Figure 4.7).

Sensitivity analyses in the revised model

a) Geographical progression

From 246 participants in the dataset, 128 had both geographical and local progression and were excluded. There were no participants who had osteoarthritis in all IPJs at baseline. Therefore, 118 participants were included in the sensitivity analysis (Figure 4.6). Of these, 93 (78.8%) participants had geographical progression at follow-up. However, this sample size was too small to assess the model in this dataset.

b) Local progression

From 246 participants in the dataset, 128 had both geographical and local progression and were excluded. There were no participants who had KL grade 4 in all IPJs with osteoarthritis at baseline. Therefore, 118 participants were included in the sensitivity analysis (Figure 4.6). Of these, 9

(8.3%) participants had local progression at follow-up. However, this sample size was too small to assess the model in this dataset.

Table 4.6: Coefficients, Odds ratios and 95% confidence intervals for the revised prognostic model for the progression of IPJ osteoarthritis

Predictor	**Odds ratio (95% confidence interval)**	**Regression coefficient**
Age (years)	1.01 (0.98 to 1.04)	0.01
BMI (kg/m^2)	1.01 (0.97 to 1.04)	0.007
Occupation (manual versus non manual)	0.70 (0.48 to 1.04)	0.35
OA at first CMCJ (yes versus no)	1.21 (0.81 to 1.79)	0.19
Family history of OA (yes versus no)	1.27 (0.83 to 1.94)	0.24
Sex (female versus male)	1.54 (1.03 to 2.32)	0.43
Race (Caucasian versus non-Caucasian)	0.74 (0.48 to 1.16)	-0.30
Intercept		
≥1 IPJs	-	1.49
≥2 IPJs	-	0.51
≥3 IPJs	-	-0.07
≥4 IPJs	-	-0.47
≥5 IPJs	-	-0.84
≥6 IPJs	-	-1.21
≥7 IPJs	-	-1.54
≥8 IPJs	-	-1.90
≥9 IPJs	-	-2.43

BMI: Body mass index; CMCJ: Carpometacarpal joint; IPJ: Interphalangeal joints; OA: Osteoarthritis
Osteoarthritis progression was defined as an increase of ≥1 KL grade in ≥1 IPJ at follow up compared to baseline

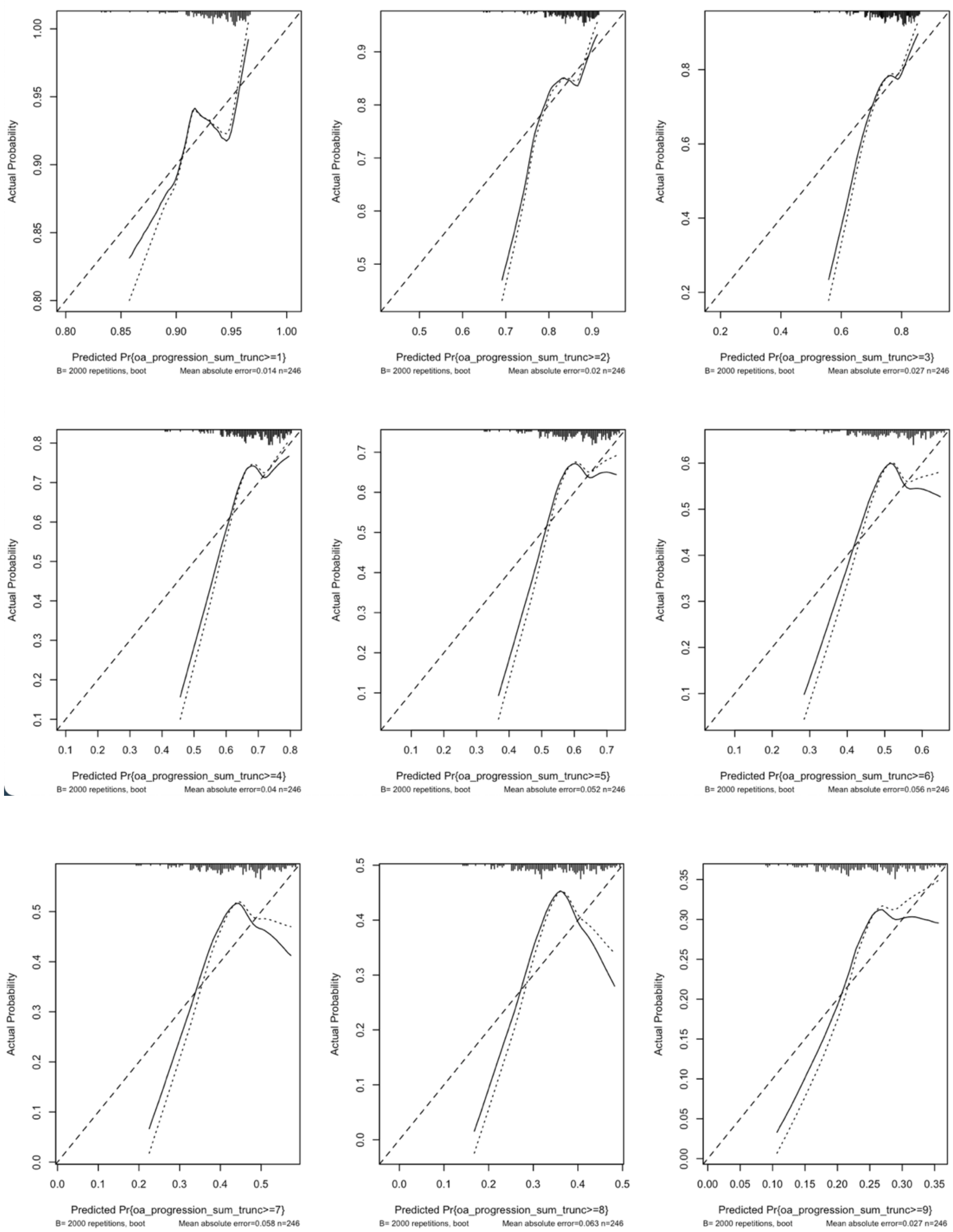


Figure 4.7: Calibration plots for each level of the outcome of the revised prognostic model

Number of IPJs with osteoarthritis progression (from top left to bottom right): a) ≥1 IPJs, b) ≥2 IPJs, c) ≥3 IPJs, d) ≥4 IPJs, e)≥5 IPJs, f)≥6 IPJs, g)≥7 IPJs, h)≥8 IPJs, i)≥9 IPJs
X axis: Predicted probability from the model
Y axis: Actual probability from the dataset
The dashed line (45° angle) represents perfect calibration.
The dotted line represents calibration of the model before correcting for overfitting.
The continuous line represents calibration of the model after correcting for overfitting through penalised maximum likelihood estimation and 2,000 bootstrap iterations.

4.6 Discussion

4.6.1 Summary

A proportional odds logistic regression model for the progression of IPJ osteoarthritis was built using the Chingford Study. No prognostic factors were found to be significantly associated with IPJ osteoarthritis progression. The model showed poor performance in the Chingford Study and poor transportability in the JoCo Project. The model was re-calibrated in the JoCo Project, though this also showed poor performance. When the model was re-calibrated in the geographical subgroup, performance improved. The model was then revised in the JoCo Project, and sex and race were included as predictors. Female sex resulted in a 1.54 (95% CI: 1.03 to 2.32) increased odds of IPJ osteoarthritis progression in n IPJs compared to <n IPJs. However, discrimination remained poor and the model was mis-calibrated.

Female sex was the only prognostic factor identified for the progression of IPJ osteoarthritis. Hand osteoarthritis is known to be more prevalent in women compared to men (26, 185). Therefore, it might be expected that female sex might also be a prognostic factor for the progression of IPJ osteoarthritis. Hand osteoarthritis is also most prevalence during the peri-menopausal age (26, 185). The median age of participants in the JoCo Project at baseline was 63.8 years, indicating that most female participants were likely to be post-menopausal. The influence of this change in female hormones might have contributed to the higher odds of IPJ osteoarthritis progression in females. The effect of menopause on osteoarthritis progression in any hand joint has not yet been analysed, whilst a systematic review assessing incident hand osteoarthritis most commonly found no association (309). Further studies should aim to better investigate the relationship between female hormones and osteoarthritis progression.

First CMCJ osteoarthritis was a strong predictor for IPJ osteoarthritis progression, in both the original model developed in the Chingford Study, and in the revised model from the JoCo Project. This model is based on the hypothesis that first CMCJ and IPJ osteoarthritis are considered to be different subsets of the same disease (311). However, the results from these prediction models suggest that prevalent first CMCJ osteoarthritis in the presence of IPJ osteoarthritis might be a risk factor for IPJ osteoarthritis progression. The results support the findings of the prediction model for incident IPJ osteoarthritis, which also found that first CMCJ osteoarthritis is a risk factor for incident IPJ osteoarthritis (Chapter 3). This suggests that hand osteoarthritis is a multi-joint disease affecting both the first CMCJ and the finger IPJs. The pathogenesis for this is not yet well understood. It is possible that the presence of first CMCJ osteoarthritis might affect the biomechanics across the hand. First CMCJ osteoarthritis is known to change the distribution of force across this joint, causing joint instability and further osteoarthritis progression (312). This could lead to changes in force across the rest of the hand, including the IPJs. However, further research is needed to better understand the biomechanics in the hand due to osteoarthritis.

The performance of the model improved in the geographical subgroup. This suggests that the definition used for IPJ osteoarthritis progression was too broad. It is possible that geographical and local progression are different subtypes of progression, with different aetiology. The systematic review (Chapter 2) found that studies more frequently measure geographical progression compared to local progression. Geographical progression was found to be more prevalent than local progression in both the Chingford Study and the JoCo Project. This suggests that IPJ osteoarthritis spreads across joints, rather than worsens at a joint which is already affected. Studies have shown there are non-random associations for the presence of OA between different joints of the hand. In particular, there are associations between a) symmetrical joints, b) the same row of joints (i.e.- joint type), and c) the same ray of joints (i.e.- within the same digit) (109, 168). These associations have been assessed based on supervised learning methods, whereby they have specifically been analysed due to anecdotal evidence that they might exist. Future research could investigate clustering patterns cross-sectionally, and longitudinally for the geographical progression of IPJ osteoarthritis. Risk factors for geographical progression versus local progression of IPJ osteoarthritis have also not yet been investigated. The prediction models in the chapter included only systematic risk factors, which might be more likely to affect a number of joints, rather than one site. The presence of localised risk factors should be studied in the future.

4.6.2 Potential limitations

Limitations with study population

The models had a low sample size, and particularly the few numbers of participants per outcome level. As sample size calculations have not yet been developed for proportional odds models, the number of candidate predictors was minimised, and therefore only five were included in the original model and seven were included in the revised model. Despite this, the numbers of participants without the event were less than ten times the number of candidate predictors in the models. The outcome levels were also truncated, to prevent sparse participant numbers across higher outcome levels. To prevent overfitting, a PMLE shrinkage method was applied to the model. However, shrinkage methods have been shown to work less well in smaller datasets and in models with low events per variable ratios, and may have contributed to the mis-calibration (313). The models are not recommended for use in clinical settings.

Participants from the Chingford Study and JoCo Project who were included in this study had osteoarthritis on their baseline radiographs. In the Chingford Study, one third of participants did not have radiographs at baseline, and of those who did, approximately two thirds had no IPJ osteoarthritis at baseline. Therefore, only a small sample of the Chingford Study participants were eligible for the current study. In the JoCo Project, almost all participants had hand radiographs at baseline. Yet, approximately two thirds of participants had no IPJ osteoarthritis at baseline. The prevalence of radiographic hand osteoarthritis in women between the ages of 45 to 64 years' old has been described as between 12% to 62%, in the Framingham Osteoarthritis Study, a population-based longitudinal studies of Americans (183). The prevalence of IPJ osteoarthritis has not yet been described in either the UK or American population. However, results from the Framingham Osteoarthritis Study suggest that the prevalence of IPJ osteoarthritis at baseline in the Chingford

Study and JoCo Project accurately represent the prevalence of IPJ osteoarthritis in the general female population. It is also unclear whether any participants received treatment for IPJ osteoarthritis either before or during the study. However, as there are no disease modifying drugs for osteoarthritis (314), radiographic osteoarthritis is unlikely to be affected by the use of localised or systemic drugs or steroid injections.

Participants included in the current study from the Chingford Study were both older and more likely to have osteoarthritis in at least one first CMCJ at baseline compared to participants without osteoarthritis at baseline. They were also more likely to have a family history of hand osteoarthritis at baseline compared to participants without radiographs and participants with radiographs but without osteoarthritis at baseline. Participants included in the current study from the JoCo Project were also older, more likely to be female, Caucasian, work in non-manual occupation, have osteoarthritis in at least one first CMCJ at baseline, and have a family history of osteoarthritis at baseline, compared to both participants without osteoarthritis at baseline. We might expect these findings, as older age and first CMCJ osteoarthritis have been shown to be risk factors for incident IPJ osteoarthritis (Chapter 3). The prevalence of hand osteoarthritis is also higher in women than in men (26), though the prevalence of IPJ osteoarthritis specifically, and across sexes, is not yet known. The difference in baseline demographics of participants included in the current study compared to those recruited to both the Chingford Study and the JoCo Project, might increase the chance of these demographics being spuriously identified as risk factors for IPJ osteoarthritis progression.

<u>Limitations with data variables</u>

Manual occupation was found to be a risk factor for incident IPJ osteoarthritis (Chapter 3), and so it could be expected that participants included in the current study might have a higher prevalence of manual occupation. Yet, in the current study, participants from the Chingford Study had a similar prevalence of manual occupation as participants without radiographs and as participants with radiographs but without IPJ osteoarthritis at baseline. Participants in the current study from the JoCo Project were found to have a lower prevalence of manual compared to non-manual occupation. This might be because osteoarthritis in joints in the hand is known to cause pain and loss of function, and may lead to people stopping manual work. For the current study, only participants with radiographic IPJ osteoarthritis were included. Though the relationship between radiographic and symptomatic hand osteoarthritis is not well understood, it is possible that participants recruited to the current study experienced loss of function and pain, preventing them from working in manual jobs. Additionally, participants recruited to the current study are older, and therefore might be less likely to have manual occupations.

Data describing a self-reported family history of osteoarthritis was described differently between the Chingford Study and the JoCo Project. In the Chingford study, it specifically described a family history of hand osteoarthritis in any of grandmother/ aunt/ mother/ father/ brother/ sister. Whilst in the JoCo Project, it described a family history of osteoarthritis in any joint, with family members not specified. This might have accounted for the higher prevalence of a family history of osteoarthritis in the JoCo Project compared to the Chingford Study at baseline. It might have also resulted in the mis-calibration and poor re-calibration of the original model in the JoCo Project.

Osteoarthritis was measured radiographically, using the KL atlas (79), in both the Chingford Study and JoCo Project. In the Chingford Study, radiographs were read by two trained readers, whilst in the JoCo Project they were read by one MSK radiologist. Though the kappa values within the Chingford Study and JoCo Project were high, the inter-observer agreement between the Chingford Study and JoCo Project has not been tested. Additionally, radiographs in the JoCo Project were read sequentially. Reading paired radiographs unblinded to time sequence has been shown to increase reproducibility and sensitivity (295). Reading radiographs without knowing the chronological order has been argued to decrease the ability of radiograph readers in detecting disease progression, specifically in risk factor studies (315). It is unknown whether the Chingford radiographs were read sequentially. Therefore, disease progression might be more accurately described in the JoCo Project compared to the Chingford Study. Participants in the Chingford Study were followed up for ten years, whilst those in the JoCo Project were followed up for between 12 to 14 years. Osteoarthritis is known to be a chronic and progressive disease, and the increased follow-up time in the JoCo Project might have resulted in the higher number of IPJs with progression when the model was revised.

There is no consensus for the diagnosis of IPJ osteoarthritis progression (Chapter 2), therefore, a broad definition was used to capture any progression. This could have resulted in poor performance of the models, with difficulty of the models discriminating between participants with and without the outcome. Therefore, sensitivity analyses with more defined outcome measurements were used. The calibration plot of the model in the geographical subgroup following model re-calibration improved (sample size too small to model in the local subgroup). This suggests that more tightly defined outcomes could improve the performance of prognostic models. Further work is needed in the field of hand osteoarthritis to better understand whether geographical and local IPJ osteoarthritis progression should be considered as different types of disease progression, and whether they might have different risk factors.

<u>Limitations with statistical analysis</u>

Time to event data was not available in either the Chingford Study or the JoCo Project. Therefore, it was not possible to determine at which time points osteoarthritis progressed. If time to event data was available, a Cox model could have been used to analyse the data. Instead a regression model was used. The rate of osteoarthritis progression could also not be calculated, and the effect of candidate predictors on the rate of progression is unknown. Future studies might benefit from assessing hand osteoarthritis progression at shorter time intervals. However, it is unlikely that radiography would be appropriate, due to increased exposure to radiation, and the need for participants to attend radiology units for the imaging to be taken. Instead, the use of examinations, questionnaires, and virtual assessments might allow for monitoring of symptomatic and/or clinical osteoarthritis progression, particularly for pain, loss of function, and nodes.

A proportional odds approach was used to develop the model, as it was thought to represent the most clinically applicable type of model (one coefficient per risk factor). When the assumption of proportional odds was tested, the results were heterogenous. When visualised graphically, an ordinal pattern was found for the means of the predictors stratified by the outcome levels. However, on further inspection, it was clear that individual means of the predictors were widely distributed, and, though an ordinal pattern exists, it was unlikely to be very strong. When the logits of outcome levels were plotted against the levels of the predictors, there was also some heterogeneity within predictors. This also suggested the assumption of proportional odds was weakly satisfied. These results could be due to a small sample size, which is difficult to model across outcome levels. A multinomial model could fit the data well, but was considered difficult to translate into future clinical practice (multiple coefficients per risk factor), and therefore this single parsimonious proportional odds model was used. Future work could consider a partial proportional odds model, allowing for non-proportional odds of a subset of candidate predictors which do not satisfy the proportional odds assumption (313, 316-319). However, large sample sizes are required (318), and partial proportional odds models often rely on repeated outcome measurements over time (318).

4.6.3 Strengths

These are the first prediction models for the progression of IPJ osteoarthritis. The original model was developed in one population-based cohort and externally validated in another. The model was re-calibrated with the aim of improving performance. This study was further strengthened by the revision of the prediction model, with the inclusion of additional candidate predictors. Including additional candidate predictors, particularly one which was found to be important (female sex), may have contributed to the small amount of mis-calibration and underfitting in the revised model compared to the original model.

4.6.3.1 Translating research to clinical practise

The original prognostic model was developed in females, and therefore should only be considered for use in females; whilst the revised prognostic model could be considered for use in both males and females. However, as both models showed poor performance, it would not be advisable to use them in clinical practice, unless they are improved. Improving these models might include developing them using larger sample sizes, and using more tightly defined outcome criteria, such as geographical IPJ osteoarthritis progression separately from local IPJ osteoarthritis progression.

Once the performance of these models are improved, further work might also consider methods to make them useable in clinical settings. For example, developing a nomogram for each ordinal outcome variable. Due to the large number of outcome variables, it might be more practical to develop electronic nomograms which can be hosted on online webpages. Additionally, decision curve analyses should be considered to determine the cost:benefit ratio of using the models. However, to my knowledge, to date no methodology currently exists to enable the decision curve analyses of proportional odds logistic regression models, and further work in this field is required. It is also likely that limited, or no, clinical data exists to inform the threshold for decision curves, and this data would be useful in informing the analyses.

4.6.4 Future research

The results suggest that sex has an effect on the risk of IPJ osteoarthritis progression. Future studies should assess IPJ osteoarthritis progression separately in different sexes, such as through stratification for sex in analyses. Further work is also needed to identify risk factors for IPJ osteoarthritis progression in males.

Osteoarthritis in the first CMCJ and the IPJs might represent a continuum of disease. Osteoarthritis in the hand is likely to be a complicated disease affecting multiple joints, with disease at one joint influencing disease at another joint. To better understand the change in biomechanics across IPJs in the presence of first CMCJ osteoarthritis, and I am involved in a future National Institute of Health grant application, through a collaboration with Wake Forest University.

5 CHAPTER 5: HAND INJURY

5.1 Chapter Aims

This chapter consists of two parts. The first part will describe the incidence, pattern and severity of hand injury, and the second part will analyse the association of hand injury with hand pain and osteoarthritis.

5.2 Introduction

Injury is well known to be a risk factor for both hip and knee osteoarthritis (320, 321). This can be either due to over-loading of the joint, or acute traumatic injury, both leading to damaged cartilage. Damaged cartilage itself increases loading to areas of the joint which previously experienced low forces, leading to cartilage breakdown and the development of osteoarthritis (322) (323). In the hands, the association between injury and osteoarthritis has not yet been well studied.

Particular groups of people might be at increased risk of hand injury, such as sports players and those with repetitive loading due to occupational exposure. In the systematic review identifying risk factors for incidence osteoarthritis, dental occupation was found to be a risk factor (chapter 2), and, in the prognostic model for the incident of IPJ osteoarthritis, again occupation was found to be a prognostic factor (Chapter 3). In the systematic review, finger fracture was a risk factor (with limited evidence) (Chapter 2), but, in the Chingford Study, the prevalence of hand injury was low, and it is likely that this prevented it from being accurately modelled in the prognostic model (Chapter 3).

When considering sporting injuries, half of acute sporting injuries presenting to orthopaedic departments are to the hand or wrist (324). In sports involving a bat or stick and a ball, such as cricket, the risk of hand injury might be even higher due to players catching balls at high speed, and the chance of fingers being struck against the hard bat handle. Indeed, during the International

Cricket Council Cricket World Cup 2011, the incidence of hand injuries was 1 per 1000 player days (129). In female cricketer in particular, injuries to the hand and wrist injury are the most common reason for time lost (325). In male cricketers, these hand and wrist injuries are most commonly fractures, with hand and wrist fractures being the third most prevalent injury type in male cricketers (326).

Despite the high prevalence of hand injuries in sports players, the exact patterns (incidence, anatomical location, type, cause, and severity) of hand injuries whilst playing sports have not yet been well studies. The popularity of cricket and the high incidence provide an ideal population in which to study these patterns, and the association of hand injury with hand osteoarthritis.

5.3 Study 1: Epidemiology of hand injury in cricketers in Victoria, Australia

5.3.1 Objective

The objective of this study was to describe the incidence, pattern, nature, and cause of hand injury within people playing cricket.

5.3.2 Methodology

5.3.2.1 Study design

To analyse the incidence, pattern and severity of hand osteoarthritis within people playing cricket, a population of cricketers is required. This could be sought from an external database, which captures the number of cricketer players across a population. Additionally, the number of cricketer players with hand injury caused by cricket and with sufficient severity to seek medical treatment is also required. Data collected on patients seeking medical treatment could be captured in primary care, such as at GPs and physiotherapists, or in secondary care, such as through routinely collected hospital data (including emergency department (ED) records). I have chosen to assess hand injuries presenting to EDs and those requiring hospital admission, in order to capture hand injuries which are severe enough to require medical treatment at secondary care facilities.

5.3.2.2 Data sources

<u>Population of cricketers</u>

In order to describe the incidence rates of cricket-related hand injuries, a population of cricketers was required. In 1909, the International Cricket Council was founded by Australia, England and South Africa (327). Since then, the popularity of cricket has grown globally, at both the recreational and elite levels (328). However, the number of cricket players within each country has not been well captured, with Australia being one of the only countries to run an annual national cricket census (329). Therefore, a population of cricketers from Australia were used for the current study.

The Australian Cricket Census has been running annually for approximately 20 years, capturing data on the number of outdoor cricket participants, per state/territory (330, 331). For a cricket player to be captured in the census, they must have played a minimum of four cricket games per week in an organised setting (such as a school or in a competitive environment) (331). Validation checks of the process through which the census is performed and its results have being independently performed by a consulting company (331).

Incidence of hand injury from playing cricket

Preventing injury from sports has been identified as an important research priority by the Centers for Disease Control and Prevention (332). To inform the prevention of injury from sports, the Sequence of Prevention of Sports Injuries (333) and Translating Research into Injury Prevention Practice (334) frameworks recommend using injury surveillance to quantify injury rates. There are few international datasets which have captured the incidence and characteristics of injuries presenting to hospitals. However, within Australia, the Victoria Injury Surveillance Unit (VISU) has been developed to collect de-identified injury surveillance data using routinely collected data in hospitals in Victoria, Australia (335).

The VISU collects data on emergency department presentations, hospital admissions, and injury deaths. These are held on three datasets: Cause Of Death Unit Record File, Victorian Emergency Minimum Dataset (VEMD), and the Victorian Admitted Episodes Dataset (VAED). Recruitment to the VEMD and the VAED, used in this chapter, are detailed in Appendix 5.1.

5.3.2.3 Reporting Guideline and Ethical approval

The reporting of the current study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (336). Ethical approval to collect and process injury data is held by the VISU. As de-identified summary data was provided by the VISU, no further ethical approval was required.

5.3.2.4 Data extraction for the current study

For the current study, summary data on cricket participation was taken from the National Cricket Census between July 2007/8 to June 2017/18 for Victoria, Australia (330). The number of cricketers over these ten years was summed to give the number of person years. The assumption was that each person played for the entire year.

Data on hand injuries related to playing cricket, presenting to hospital between July 2007/8 to June 2017/18, were taken from the VEMD and VAED held by the VISU. During my DPhil, I was able to set up a collaboration with the VISU, allowing me to use summary data from the VEMD and the VAED. Information on how data was extracted by VISU is detailed in Appendix 5.2.

5.3.2.5 Statistical analysis

All analyses were performed in Microsoft Excel version 16.49.

Annual incidence rates of hand injuries per 10,000 cricketer years were calculated for all hospital presentations (ED presentations and hospital admissions), ED presentations (from the VEMD), and hospital admissions (from the VAED) . The denominator was the total number of cricketers over 10 years, from the National Cricket Census (330). The numerator was the number of cricketers recorded as having cricket-related hand and wrist injuries over 10 years, from the VISU. This was defined as:

$$\frac{total\ number\ of\ hand\ and\ wrist\ injuries\ over\ 10\ years}{total\ number\ of\ cricketers\ over\ 10\ years} * 10{,}000$$

The VISU provided summary data, stratified by sex and age categories, on the number of hand and wrist injuries. Summary data for the total number of cricketers over 10 years was taken from the National Cricket Census (330). Data stratified by sex and age categories was not available from the National Cricket Census, so absolute numbers are provided (330).

Summary data was used from the National Cricket Census (330), and the VEMD and VAED, as individual patient level data was not available. Therefore, it was not possible to individually match cricket players between the National Cricket Census (330), and the VEMD and VAED.

Data was provided by the VISU for anatomical location of injury for the VEMD only (harmonisation of data shown in Appendix 5.3). Data was provided on the type of injury and on the cause of injury for both the VEMD and the VAED. I harmonised data between the VEMD and the VAED for the type of injury and on the cause of injury (harmonisation of data shown in Appendix 5.3).

5.3.3 Results

5.3.3.1 Study participants

Of the 9,188 hospital presentations, 5,327 (58.0%) were ED presentations, and 3,861 (42.0%) were hospital admissions. The incidence rate for hand or wrist injury resulting in hospital presentations was 34.2 out of 10,000 cricketer years, and specifically for ED presentations it was 19.8 out of 10,000 cricketer years, whilst for hospital admissions it was 14.4 out of 10,000 cricketer years. Across the decade, there was a downward trend of annual incidence rates for all hospital treatments, ED presentations, and hospital admissions (Figure 5.1, Appendix 5.4). The ratio of ED presentations to hospital admissions was 1.4:1. Of all the hospital admissions, length of stay was <2 days for 3,377 (87.5%).

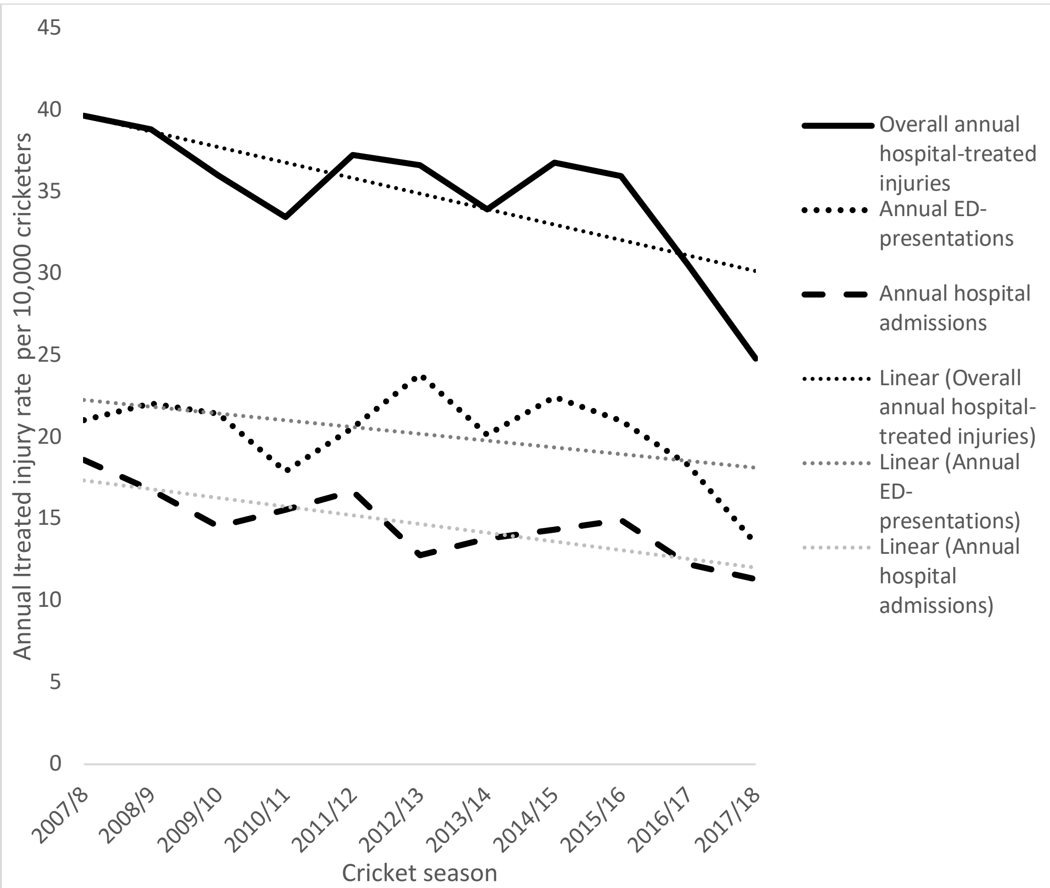
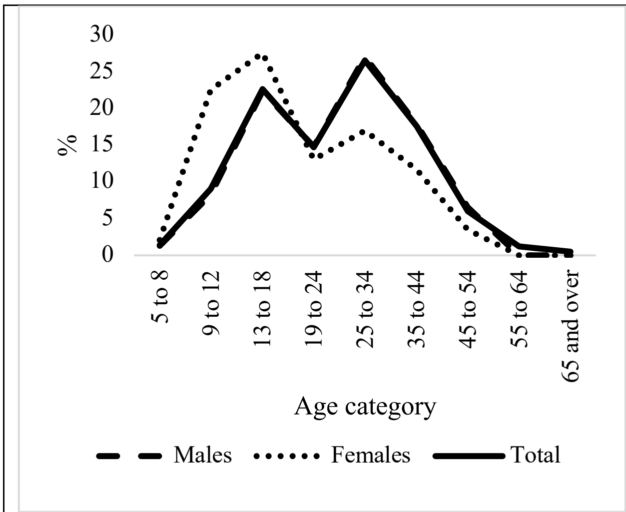


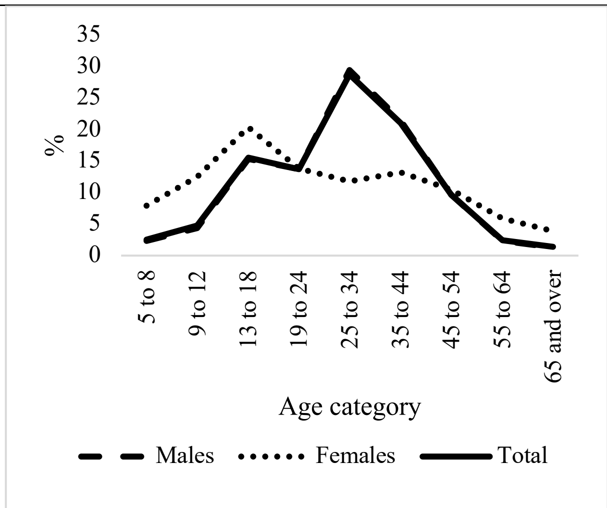
Figure 5.1: Trends in hand and wrist injuries presenting to hospital, per 10,000 cricketers, between July 2007/8 to June 2017/18 cricket seasons

ED: Emergency department. All incidence rates are shown with linear trend lines overlaid.

Within ED presentations, 5,122 (96.2%) were males, and 205 (3.8%) were females. Similarly, within hospital admissions, 3,709 (96.1%) were males, and 152 (3.9%) were females. The 25 to 34 years age group most commonly presented to EDs (1,416 (26.6%,); Figure 5.2a), and were also most commonly admitted to hospital (1,112 (28.8%); Figure 5.2b). When stratified by sex, in males this remained true (ED presentations: 1,368 (27.1%); hospital admissions: 1,094 (29.5%; Figures 5.2a and 5.2b: lines overlie each other on graph). In contrast, females aged 13 to 18 years were most commonly treated in EDs (78 (27.6%,); Figure 5.2a), and admitted to hospital (31 (20.4%); Figure 5.2b).



5.2a. Frequency of ED presentations by age, total and stratified by sex



5.2b. Frequency of hospital admissions by age, total and stratified by sex

Figure 5.2: Frequency of hospital treatments by age category, for all patients and stratified by sex

ED: Emergency department. Note the total line overlies in the male' in both figures

5.3.3.2 Anatomical locations of injuries

Within ED presentations, the thumb and little finger were the most common sites of injury (thumb: 878 (16.5%); little finger: 836 (15.8%) (Figure 5.3a). When stratified by sex, in males, there were 838 (16.9%) thumb injuries, making it the most commonly injured anatomical location. Whilst in females, there were 48 (17.1%) little finger injuries, making this site the most common (Figure 5.3a). When stratified by age category, in the youngest age category (five to eight years), injury to the thumb was the most prevalent anatomical location (17 (23.0%); Figure 5.3b). As age increased, the prevalence of thumb injuries decreased, whilst the prevalence of little finger injuries increased. In the oldest age category with this data (55 to 64 years), injury to the little finger (9 (14.1%)) was the most common anatomical location (Figure 5.3b). However, there was a large amount of missing data throughout. As summary data was provided, it was not possible to investigate patterns to the missingness of data. If more granular data was available, the patterns of missing data would have been analysed to assess whether missing data was MCAR, MAR, MNAR (handling missing data has been discussed in Chapter 3- section 3.3.8).

5.3.3.3 Types of injuries

ED presentations

Fractures (2,386 (44.8%)) and dislocations (1,704 (32.0%)) were the most common type of injuries within ED presentations (Figure 5.3c). If a male presented with an injury, this pattern remained (fractures: 2,283 (45.3%); dislocations: 1,593 (31.6%)), but if a female presented with an injury this was more likely to be due to dislocations (111 (39.2%)) than fractures (103 (36.4%)) (Figure 5.3c). When stratified by age, across all age groups, fractures were the most common injury type, followed by dislocations (Figure 5.3d). However, if a younger player presented with an injury, they were also more likely than players in other age categories to have a superficial injury (five to eight years: 7 (9.5%) (Figure 5.3d). Similarly, if an older player presented with an injury, they were more likely than players in other age categories to have an open wound (55 to 64 years: 12 (18.8%)) (Figure 5.3d).

Hospital admissions

The most common injuries within hospital admissions were fractures (2,032 (52.5%)) and dislocations (699 (18.1%)), in all participants (Figure 5.3c). This pattern remained in both males (fractures: 1,960 (52.8%); dislocations: 671 (18.1%)), and females (fractures: 72 (47.4%); dislocations: 28 (18.4%)) (Figure 5.3c). When stratified by age, fractures were still the most frequent type of injury requiring admission across all age groups (Figure 5.3d). In younger players, they were more likely than those in other age groups to require admissions for open wounds (five to eight years: 33 (34.0%); nine to twelve years: 26 (14.1%)) (Figure 5.3d); and in older players, they were more likely than those in other age groups to require admissions for muscle injuries (55 to 64 years: 18 (19.1%); ≥65 years: 6 (11.3%)) (Figure 5.3d).

5.3.3.4 Causes of injuries

ED presentations

Players most commonly presented to EDs with hand and wrist injuries due to being hit by the ball (4,162 (78.1%)). When stratified by sex, hitting remained the most common cause of injury in both male (3,941 (78.1%)) and female (221 (78.1%)) players (Figure 5.3e). Hitting injuries were the most common cause of injury for all age groups (Figure 5.3f). Younger and older players presenting to EDs were also likely to present due to falling injuries, compared to players in the middle age categories (five to eight years: 25 (33.8%); ≥65 years: 7 (28.0%) (Figure 5.3f).

Hospital admissions

The mechanism of injury leading to hospital admission mirrored those seen in ED presentations. Being hit on the hand or wrist by the cricket ball was the most common cause of injury leading to hospital admission (2,187 (56.6%)), and this was true in a sex stratified analysis (males: 2,122 (57.2%); females: 65 (42.8%)). In females, there was also a high percentage of admissions for hand injuries from falls (48 (31.6%)) compared to in males (Figure 5.3e). When stratified by age, hitting was the most common cause of injury in all age groups except for age ≥65 years, where falling was the most common cause of injury (31 (58.5%)). Falling was also of high prevalence in the youngest age category of five to eight years (21 (21.6%)) (Figure 5.3f).

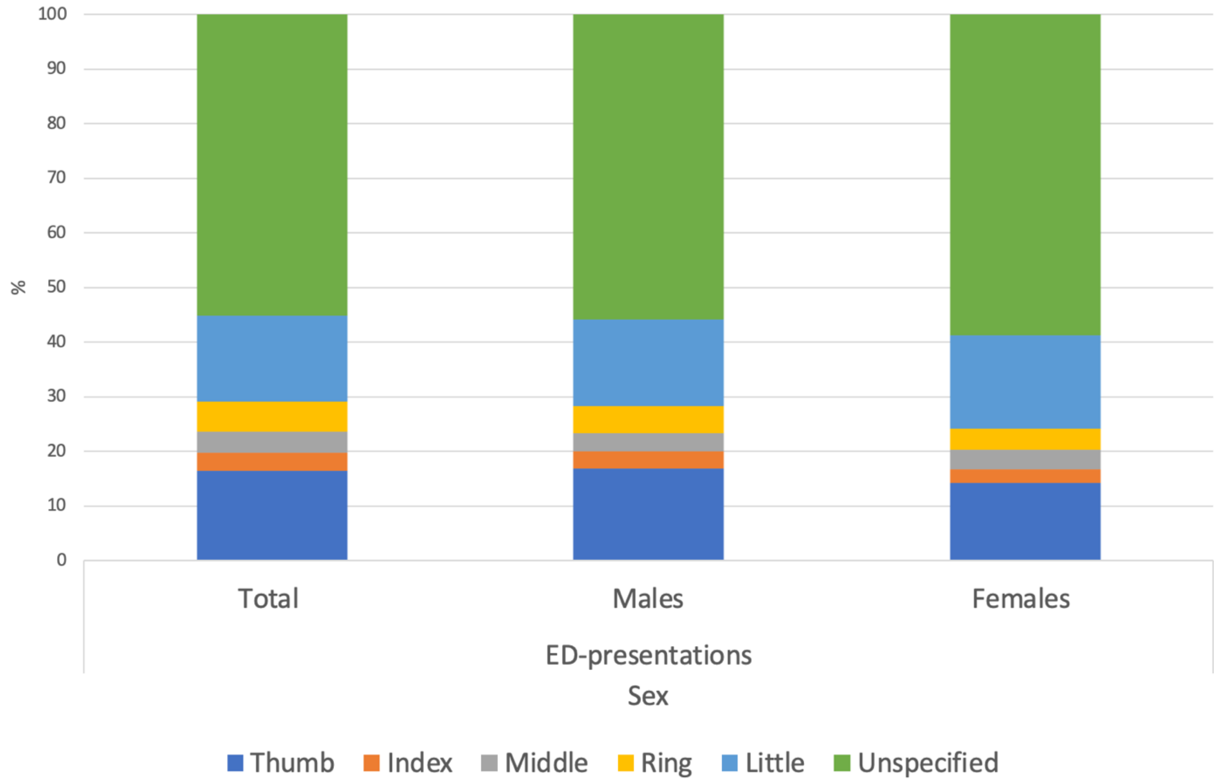


Figure 5.3a

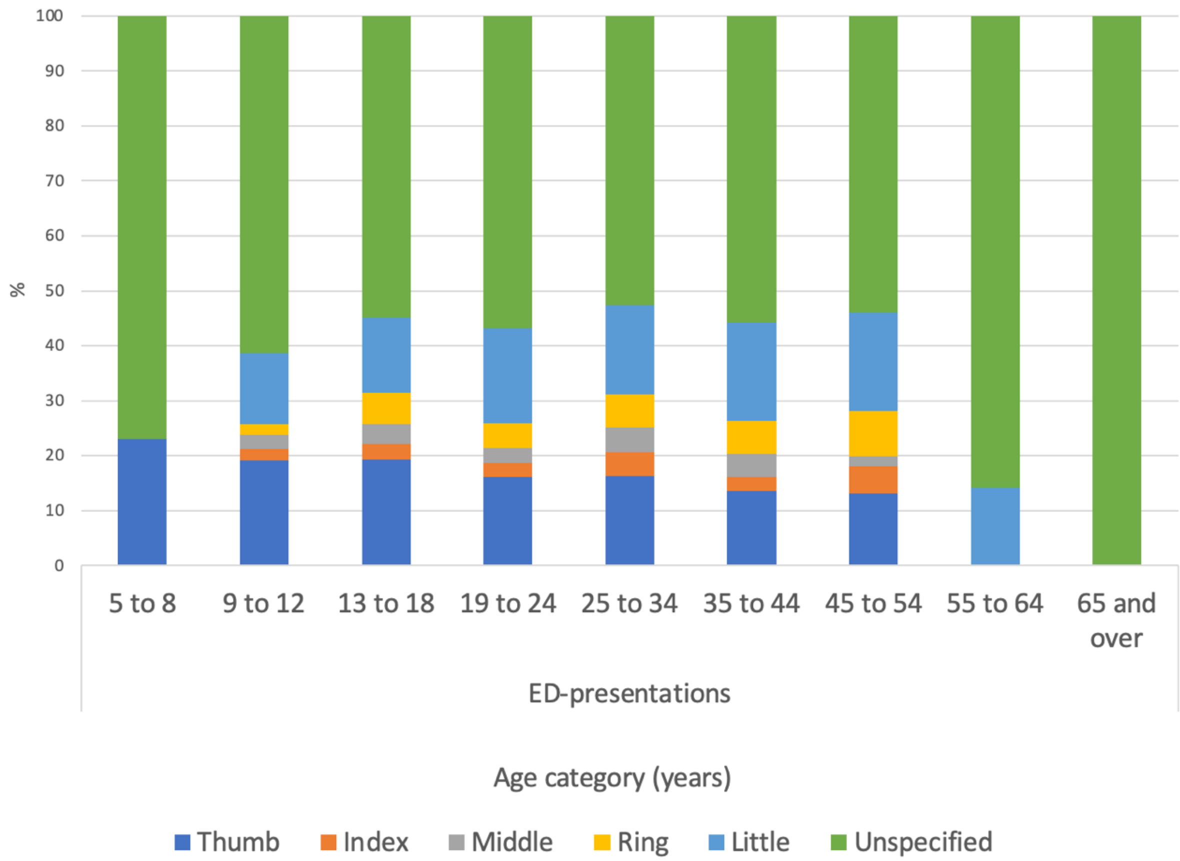
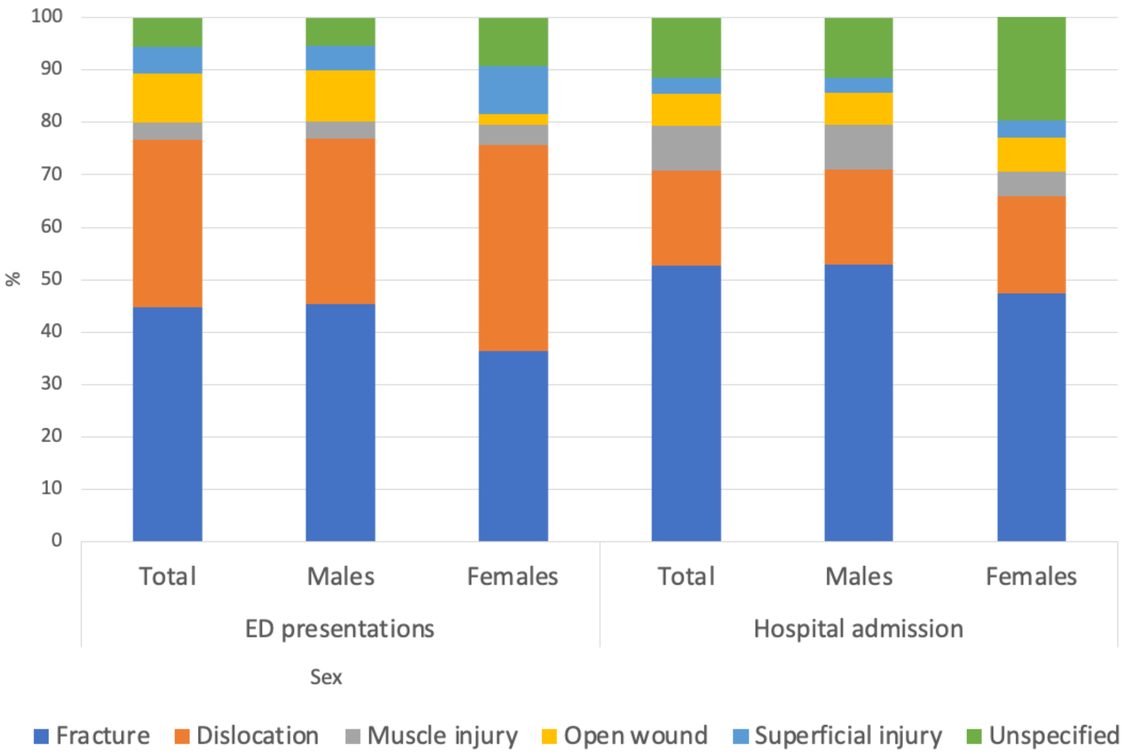


Figure 5.3b



100
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Total
Males
Females
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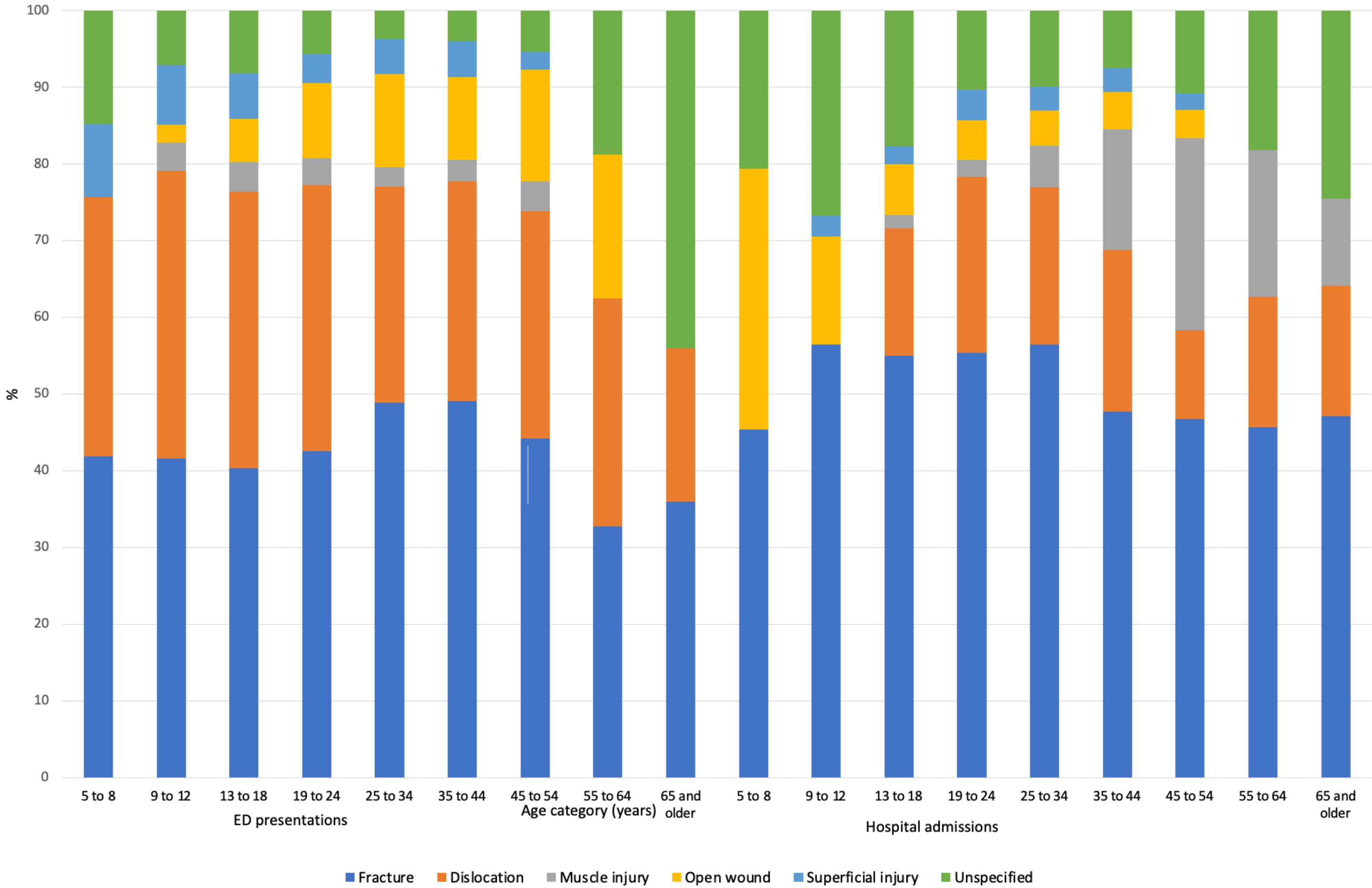
ED presentations
Hospital admission
Sex
Fracture
Dislocation
Muscle injury
Open wound
Superficial injury
Unspecified

Figure 5.3c



100
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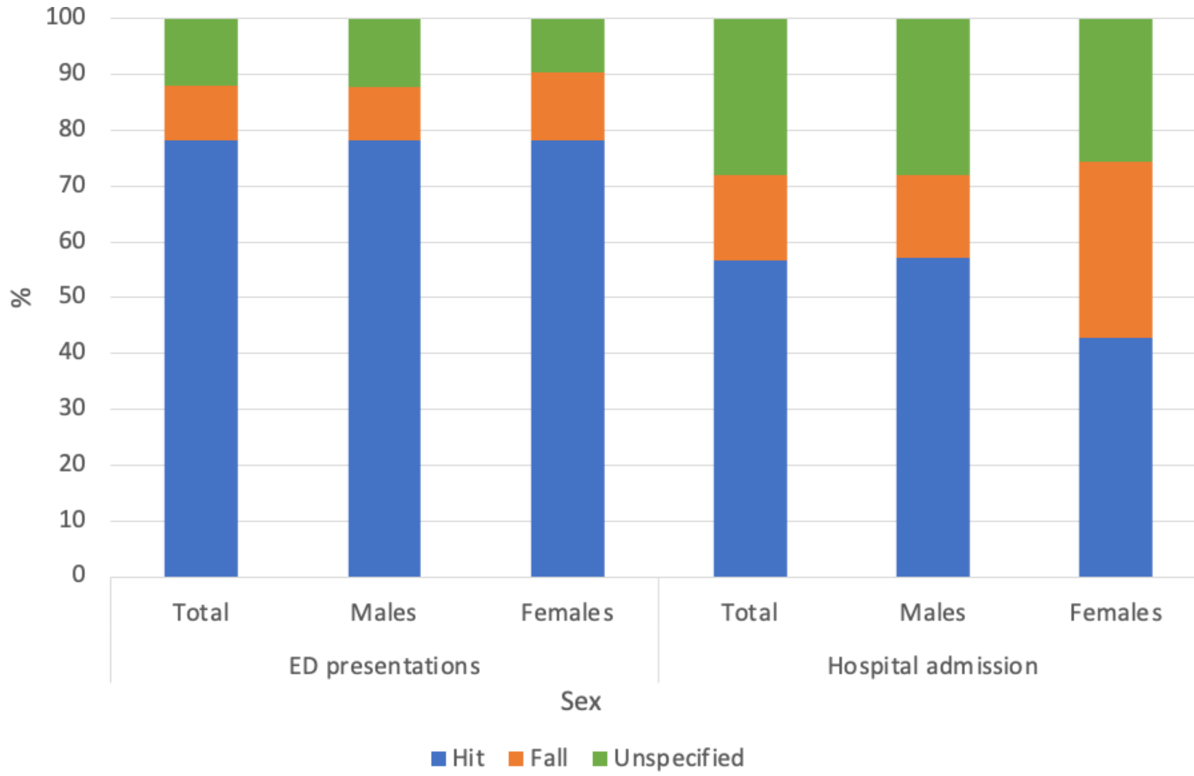
5 to 8
9 to 12
13 to 18
19 to 24
25 to 34
35 to 44
45 to 54
55 to 64
65 and older
ED presentations
Age category (years)
Hospital admissions
Fracture
Dislocation
Muscle injury
Open wound
Superficial injury
Unspecified

Figure 5.3d


100
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Males
Females
Total
Males
Females
ED presentations
Hospital admission
Sex
Hit
Fall
Unspecified

Figure 5.3e

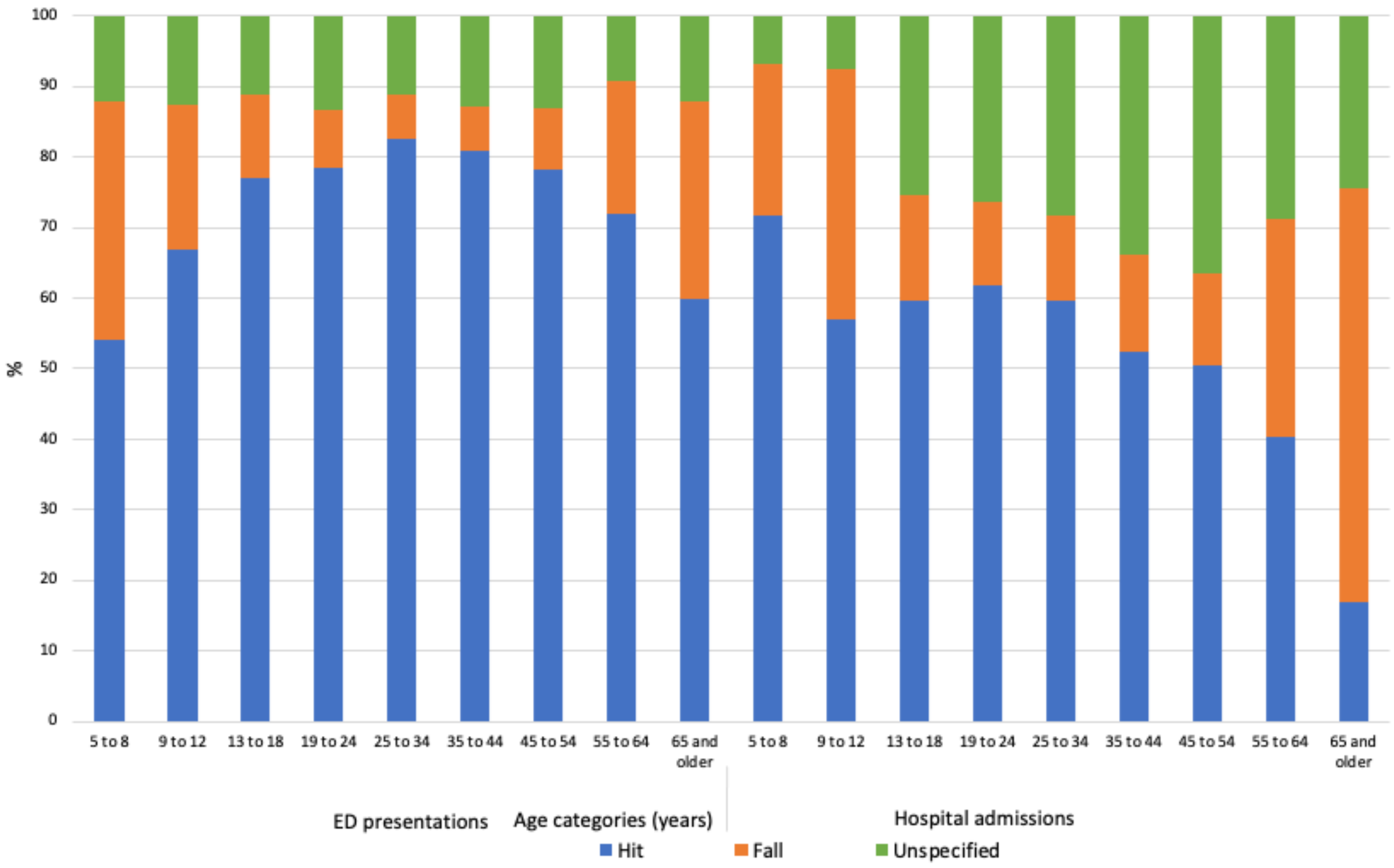

Figure 5.3f

Figure 5.3: Anatomical location, type and cause of hospital-treated hand and wrist injuries between July 2007/8 to June 2017/18 inclusive, stratified by sex and age-group

a) Anatomical location of injury, total and stratified by sex. b) Anatomical location of injury, stratified by age category. c) Type of injury, total and stratified by sex. d) Type of injury, stratified by age category. e) Cause of injury, total and stratified by sex. f) Cause of injury, stratified by age category.

ED: Emergency department

5.3.4 Discussion

5.3.4.1 Summary

Over the 10 years, there was a decline in hand and wrist injuries resulting in hospital presentations. This showed an overall decreasing trend. It is difficult to know the exact reason for this decline, though the expansion of injury prevention programmes could have been responsible. During the 2014/15 season, there was a spike in overall hospital presentations, and in both ED presentations and hospital admissions. This is thought to be due to increased awareness of injury reporting, after the 2014 injury-related death of Phillip Hughes, a young Australian test cricketer (337). There was widespread increase in injury prevention programmes, in the immediate years following his death (338). These focussed on head injury and standards for cricket helmets, though it is likely that other types of cricket-related injuries, including those in the hand, were also considered (339).

Admission to hospital is a marker of injury severity and complexity. The incidence rate of hospital admission was 14.4 per 10,000 cricketer years. This is much higher than the reported incidence rate of hospital admission for any cricket-related injury in New Zealand cricketers, which is reported as 3.9 per 10,000 cricketer years (340). However, the authors of the study from New Zealand suggest their findings have underreported the incidence rate, perhaps as they used ICD codes from hospital discharge summaries to identify cases, which might be inaccurate or contain large amounts of missing data (340). In the current study, 42.0% of all hospital presentations led to hospital admission, and the ratio of 1.4:1 ED presentations to hospital admissions indicates that a high number of hand injuries presenting to hospital were severe enough to require inpatient treatment. This is significantly higher than the 11:1 ratio reported in a community survey of all sports injuries in La Trobe Valley, Victoria (341), suggesting that cricket-related hand injuries which present to hospital are more severe than other types of sports injuries, and as such are less likely to be fully managed in EDs. However, in the majority of patients, hospital admission was for <2 days. Therefore, although hand injuries were often severe enough to require inpatient management, this could be done quickly.

The absolute number of male cricket players presenting to hospital was much higher than the absolute number of female cricketers presenting to hospital. This might be due to the higher number of males, compared to females, playing cricket, though it was not possible to calculate sex specific incidence rates as sex specific cricket participation numbers have not been reported in the Census (330). Similarly, patients were mostly commonly aged 25 to 34 years, though again it was not possible to calculate age specific incidence rates. These findings correspond with an epidemiological study reporting cricket-related injuries in American EDs, where 68.5% patients were aged between 20 to 39 years (342). This age group could be at increased injury risk due to higher forces applied when bowling and batting, resulting in both higher stress across joints (causing repetitive microtrauma), and faster moving balls which could cause acute injuries.

The thumb and little finger were the most commonly injured anatomical sites. A recent study of cricket-related hand fractures and dislocations, taken from the England and Wales Cricket board (EWCB) data between 2010 to 2014, reported the index and little fingers to be the most frequently affected sites (343). Both that study and our own, indicate that cricket-related hand injuries most commonly occur in the peripheral sites of the hands, compared to in the middle fingers. These results suggest that injury prevention strategies should target peripheral hand digits. Such strategies could include the use of personal protective equipment, such as gloves. In a review of cricket-related injuries, a lack of protective equipment was identified as a risk factor for such injuries (344). Though this review was published over twenty years ago, at present only batsmen and wicketkeepers wear gloves when playing cricket. The use of gloves in fielders has not yet been studied, despite all cricketers having to field. In wicketkeepers, the only cricket players allowed to wear gloves, the prevalence of hand or wrist injury is lower than in batsmen or bowlers/ fielders (345). In baseball, where fielders wear gloves, there is also a lower incidence of hand injuries, injuries from being hit by the ball, and fractures, compared to the current study (346). This suggests gloves might provide adequate protection from hand injuries.

Fractures were the most common injury type in both players presenting to EDs and players requiring hospital admissions. This might be expected, as fractures are considered to be some of the most severe acute hand injuries, often requiring hospital-based management. A higher proportion of injuries requiring hospital admission were due to fractures, compared to the nature of injuries presenting to EDs. This suggests they are the most severe type of injuries, agreeing with the study of EWCB cricketers, where 13.8% required surgery (343). A recent systematic review of adult athletes with hand fractures in the phalanges and metacarpals, has shown good short-term outcomes, with a 100% return to play after a mean 3.75 week follow up (347). However, in the long-term, direct interphalangeal joint injuries, such as fractures, could increase the risk of osteoarthritis (348), and the next study in this chapter will investigation this association.

Hitting was the most common cause of injury presenting to EDs across all participants, all age groups and all sexes. This is likely to occur when players hit the ball with the bat, supporting a study of elite English and Welsh cricketers, which reported hand injuries where are most common in batsmen (345). Hitting injuries might also occurs whilst catching the ball during fielding, causing a hitting mechanism of the ball against the hand. This has been found in baseball players, another stick and ball sport, where being hit by the ball was the most common cause of injury (346). However, in patients aged over 65 years' old and requiring hospital admission, falling injuries were most common. Though the reason for this has not been studied, it could be due to poorer coordination, dexterity and balance in older people compared to younger people. My study suggests that injury prevention strategies in younger cricketers could focus on limiting the force experienced from fast moving balls, whilst in older cricketers they could focus on preventing falls. Prevention strategies to limit this could include neuromuscular and proprioception training, which have been found to be effective in preventing injury in the lower limbs (349).

5.3.4.2 Potential Limitations

Limitations with study population

The majority of patients in this study were male. This reflects the large population of male cricketers (330). Though female cricketers were included in this study, they represent a very small percentage of cricket players and patients requiring hospital treatment. However, it would not be possible to generalise the results of this study to the female participants of the Chingford Study (Chapters 3 and 4), as these represent different populations, with different demographics. It was also not possible to calculate sex or age specific incidence rates, as data from the National Cricket Census was not stratified by sex or age.

This study included cricketers who presented to hospital with hand or wrist injury. Therefore, cricketers who experienced hand injuries and were either treated at the field, at other locations (such as GPs or by physiotherapists), or who self-treated, were not captured in this study. In New South Wales, the largest state in Australia, only 8.9% of players with injuries from organised sports were treated in hospitals (350). Instead, over one third of players self-treated, whilst a large proportion sought treatment from general practitioners (15.6%) and even more from physiotherapists (26.6%) (350). This study might underrepresent the true incidence of acute cricket-related hand injuries. Further work is also needed to ascertain whether there is a differential presentation of types of injuries presenting to hospital compared to those managed in primary care; it is likely that more severe injuries, such as fracture, present to hospitals and therefore would be over-represented in this study.

Limitation with data collection and variables

Summary data was provided from the National Cricket Census and from the VISU. Therefore, it was not possible to individually match patients across datasets. It is possible that one player could have presented with multiple first presentations of different hand or wrist injuries, with each of these first presentations being recorded in the VEMD/ VAED. It is also possible that cricket players from Victoria might sustain a hand or wrist injury from playing cricket whilst playing out of the state, and therefore be managed in a hospital outside of Victoria. This would not be captured by the VISU. Likewise, it is possible that cricket players who are not from Victoria but are playing cricket in Victoria when they sustain a hand or wrist injury are treated in a Victoria hospital and are therefore captured by the VISU, but not in the National Cricket Census for Victoria. Therefore, though annual injury incidence rates are calculated, there could have some inaccuracies. Similarly, the age distribution of cricketers requiring hospital treatment for hand and wrist injuries was available from the VISU though not from the census. Therefore, it was not possible to determine the rates of injury per age category. It is also clear that there were few patients being treated in hospital in the youngest and oldest age categories. This means results for these age categories might be unreliable with large margins of error.

A validation study has been performed for the VEMD, showing there is a high rate of error (351). It is therefore possible that data used in the current study to assess ED presentations could have been incorrectly captured, and not accurately reflect the nature of hand and wrist injuries which cricket players present with to EDs. No validation studies have been performed for the VAED. The VAED was coded using the ICD-10-AM codes, yet, when ICD-10 codes have been used in EDs (for the VEMD), it is estimated that one third of sports injuries are inadequately coded (351). A validation check could not be performed as part of this study, as another dataset was not available, but future work should focus on validating data in the VAED.

The data was acquired from routinely collected hospital data. Using routinely collected hospital data to quantify the scope of sports injury is thought to under represent the true incidence, due to a lack of detailed information (350). In particular, there were large amounts of missing data (over half of the data) for the anatomical location of injury, and responses only included fingers and no other sites in the hand or wrist (such as the palm or metacarpals, or the carpus or carpal bones). Therefore, the true incidence of injuries at different anatomical sites of the hand and wrist might not be accurately captured in this study. It was also not possible to separate injuries based on anatomical location within fingers, for example the IPJs from the first CMCJ or the metacarpophalangeal joints despite DIPJs being more peripheral and perhaps at higher risk of injury. The pattern of missing data could also not be assessed, as only summary data was provided by the VISU, and it was not possible to ascertain whether there were differential patterns between players with and without missing data.

There was a change in the inclusion criteria for the VEMD and VEAD from 2012, whereby for ED presentations lasting over four hours cases were counted in the VEMD only (prior to 2012, they were coded in the VAED only). This was implemented through a 'four hour rule', based on the UK model, through which patients had to either be discharged home or admitted to a ward (including a new 'ED ward') within four hours, to prevent overcrowding and decrease patient mortality (352). This might have caused the 2012/13 spike in the total number of ED presentations, and a drop in the cases requiring hospital admission. Though it reflects the nature of change within healthcare, it does affect the ability to measure patient flow over time, limiting comparisons pre and post 2012.

Though this study focussed on hand and wrist injuries in cricket players, it is possible that these injuries were not the reason for hospital presentation. It is possible that other more serious injuries, such as those to the head, could have caused players to present to hospitals, and at that time they were concomitantly treated for a hand or wrist injury. A study assessing the location of all injuries in female cricket players presenting to hospital, from the VISU, has shown that players most commonly present to hospitals due to head injuries, followed by hand or wrist injuries (325). Specifically, head injuries are the most common type of injury seen in female cricket players in EDs, and are also the most common reason for hospital admissions (325). Therefore, it is possible that the severity of hand or wrist injuries is over-estimated in this study, and in future studies this would be better analysed by assessing the overlap between hand or wrist and other injuries, and by defining the index injury necessitating hospital presentations.

5.3.4.1 Strengths

This is the largest study to date that characterises cricket-related hand injuries which present to hospitals for treatment. It captures injuries treated both in EDs and also requiring hospital admission, a marker of injury severity. This study also includes elite and recreational cricket players, both sexes, and a large range of ages, capturing the spectrum of cricket players. Furthermore, the inclusion of all cricketers and all hospital treated injuries across one state increases the chance of the entire population being captured.

5.4 Study 2: Association between hand injury and osteoarthritis

5.4.1 Objective

The objective of this study was to assess whether cricket players with significant hand injury have a later increased risk of hand osteoarthritis.

5.4.2 Methodology

5.4.2.1 Study design

To analyse the relationship between hand injury with hand osteoarthritis in cricketers, there are two possible study designs which can be used. The first is a cohort study, in which cricketers with and without significant hand injury are identified and the prevalence of osteoarthritis in those with compared to those without injury is assessed. This could be performed either prospectively, in which cricketers with and without significant hand injury could be recruited and then observed over a prolonged period of time to identify those who develop osteoarthritis. Alternatively, a retrospective design can be used, in which cricket players with and without hand osteoarthritis are recruited and study investigators assess whether or not they had a significant hand injury historically. The second study design which could be used is a case-control study, in which the cases are cricketers with hand osteoarthritis and the controls are cricketers without hand osteoarthritis. Study investigators then aim to determine the possible explanatory variables (exposures) for hand osteoarthritis.

For the current study, as both the exposure and outcome variables have already been determined from the outset (exposure variable: significant hand injury; outcome variable: hand osteoarthritis), a cohort design would be the most suitable design. As prospective cohort studies require a prolonged time period, a retrospective design was thought to be most suitable for my DPhil.

5.4.2.2 Data sources

In order to study the association between a history of significant hand injury and hand osteoarthritis, a cohort of cricket players is required, who have been followed up for a prolonged period of time, sufficient enough for osteoarthritis to develop.

The England and Wales Cricket Board

In 1997, the EWCB was formed, to govern cricket playing across England and Wales. The EWCB holds a registration database of all cricket players across England and Wales, who have, at some point, signed up to play cricket with any cricket league club across England or Wales. This means registration details both current and former cricket players are held on the database. Players who have registered on this database can consent to be contacted for cricket-related research.

The Cricket Health and Wellbeing Study

In 2017, the EWCB database was used to recruit current and former cricket players to a new study, the Cricket Health and Wellbeing Study (CHWS). The CHWS was developed to investigate health and well-being in cricketers by assessing a) cricket-related injury, b) osteoarthritis and joint pain, c) general health and the prevalence of disease, d) physical activity, and e) resilience, quality of life and flourishing. To be eligible for the CHWS, cricketers must have been aged at least 18 years' old and must have played at least one season of cricket at the time of the CHWS recruitment. Recruitment to the CHWS is detailed in Appendix 5.5.

5.4.2.3 Reporting Guideline and Ethical approval

Reporting of the current study followed the STROBE checklist (336). Ethical approval for the CHWS was sought from the NHS Health Research Authority, London Stanmore Research Ethics Committee (REC 15/LO/1274), and no further approval was required for the current study.

5.4.2.4 Data extraction for the current study

Data on self-reported history of severe hand injury, doctor diagnosed hand osteoarthritis, and chronic pain were taken from the CHWS. Additionally, a number of potential confounders (age, length of cricket participation, playing standard, and handedness whilst playing cricket) were taken from the CHWS. Information on how this was captured in the CHWS is detailed in Appendix 5.6. During my DPhil, I developed a collaboration with the CHWS, allowing me to analyse CHWS data for the current study.

5.4.2.5 Statistical analysis

All analyses were performed in Statistical Package for the Social Sciences version 26. Data was provided by the CHWS, and I transformed these as below:

<u>Outcome variables</u>

1. <u>Hand osteoarthritis:</u> Hand osteoarthritis was extracted as 'Yes' versus 'No' for each hand. Hand osteoarthritis data was extracted for all cricketers (i.e.- both current and former cricketers).

2. <u>Chronic hand pain:</u> Chronic hand pain was extracted as 'Yes' versus 'No' for each hand. Hand pain data was extracted for former cricketers only, to capture chronic pain. Data was not extracted for current cricketers to minimise confounding by pain from any recent cricket-related injury.

<u>Subgroup analysis</u>

a) <u>Dominant hand</u>

The dominant hand might be more likely to experience repetitive loading and microtrauma, due to frequent use.

b) Non- dominant hand

The non-dominant hand might be more likely to experience acute traumatic injury, due to less frequent use and perhaps being less well trained than the dominant hand.

All cricketers (current and former) who used the ‘Don’t know’ response option or identified as using ‘Both’ hands, or had missing data for the handedness question were excluded from the subgroup analysis

Explanatory variable

Hand injury: A history of significant cricket-related hand injury was categorised into ‘Yes’: if a history of having at least one injury was recorded in the CHWS, or ‘No’: if there was no history of having at least one injury was recorded in the CHWS (count of 0).

Potential confounders:

From the systematic review (Chapter 2) and the prediction model for the incidence of IPJ osteoarthritis (Chapter 3), age is known to be a risk factor for the incidence IPJ osteoarthritis, and was likely to be a confounder in this analysis. Similarly, exposure to playing cricket was likely to be a confounder due to an increased risk of both repetitive microtrauma and acute injury as exposure increased. Therefore, three confounders, which the CHWS had data for, were identified for the analysis:

1. Age
2. Length of cricket participation: Taken from the number of seasons of cricket played
3. Highest standard of cricket played: Highest standard of cricket played was categorised into higher standard: ‘International/ County or premier league/ Academy/ County-age-group’, or lower standard: ‘University/ School/ Village or social’.

As participants could have a history of significant cricket-related hand injury and hand osteoarthritis or chronic hand pain in either or both hands, a hand-level analysis was performed. Therefore, each participant was counted twice (once for the right hand, and once for the left hand) by stacking the dataset. Data on the exact anatomical location of the hand injury (i.e.- joint level data) was not collected in the CHWS, and therefore it was not possible to link joint specific data between the site of injury and the site of osteoarthritis and chronic pain. However, as first CMCJ osteoarthritis was found to be a risk factor for incident IPJ osteoarthritis (Chapter 3), it is possible they are representing one disease process and can be analysed together for the purposes of this study.

Logistic regression was used to assess the relationship between a history of significant cricket-related hand injury with ipsilateral hand osteoarthritis (i.e.- right hand injury with right hand osteoarthritis and left hand injury with left hand osteoarthritis) in all cricket players (i.e.- current and former cricketers), and between ipsilateral hand injury with ipsilateral chronic hand pain (i.e.- right hand injury with right chronic hand pain and left hand injury with left chronic hand pain) in former cricketers only. Unadjusted OR and 95% CIs were reported for each outcome. All analyses were then adjusted in a pre-planned order, first for age, and then additionally with length of cricket participation, and then additionally with highest standard of cricket played. There was no evidence that underlying assumptions were not satisfied (the variables appeared to provide independent associations (no excessive signs of collinearity), linear relationship between continuous explanatory variables and the logit transformation of the outcome, no outlier data in any continuous explanatory variables).

<u>Missing data</u>

All variables were assessed for missingness. If ≤5% of data was missing, data on participants for which there was complete data was used (233, 272, 273). If >5% of data was missing, and missingness was thought to be either MCAR or MAR, MICE was used (as described in Chapter 3, section 3.3.8).

In the current study, 2.5% of participants had missing data, so analysis was performed using complete case data (Figure 5.4)

'Don't know' responses

Participants who used the 'don't know' response option for the initial injury question, or the initial osteoarthritis question, or the initial pain, discomfort or joint problems question, or the highest standard of cricket played question were excluded from the current study.

Subgroup analysis

Data on handedness was extracted from the CHWS. Handedness was defined by the hand used to bowl or throw (right or left hand), and transformed into 'dominant hand': the hand identified to bowl or throw; or 'non-dominant' hand: the hand not identified to bowl or throw.

Seventeen cricketers (current and former) were excluded from the subgroup analysis (current cricketers: 1 'Don't know' response, 0 'Both' responses, and 4 missing responses; former cricketers: 0 'Don't know' responses, 8 'Both' responses, and 4 missing responses). The 12 former cricketers who used the 'Don't know' response option, identified as using 'Both' hands, or had missing data for the handedness question were excluded from the subgroup analysis when assessing the relationship between a history of significant cricket-related hand injury and hand pain.

Data on handedness was used to transform each of the variables for a history of significant cricket-related hand injury, hand osteoarthritis and chronic hand pain into 'dominant hand' or 'non-dominant hand', to correspond with hand dominance defined by the hand used to bowl or throw.

5.4.3 Results

5.4.3.1 Study participants

Of 2,294 CHWS participants, 223 (9.7%) were aged below 30 years and ineligible for the current study. There were 126 (6.1%) ‘Don’t know responses and these were excluded (Figure 5.4).

1,893 participants were included in the current study, of which 844 (44.6%) were former cricketers, and 1,049 (55.4%) were current cricketers. The mean age of all participants was 50.2 years (SD: 10.9); mean length of cricket participation was 30.9 seasons (SD: 14.6); and a higher standard of play was reported in 387 (36.9%) of players.

Of all cricketers, 1,024 (98.1%) were male (Table 5.1). The number of male participants, mean age, mean BMI and the distribution of ethnicity between those with and without hand injury were similar (Table 5.1). The proportion of current smokers was also similar between the two exposure groups, though participants with a history of significant cricket-related hand injury were also more likely to be former smokers, whilst those without a history of significant cricket-related hand injury were more likely to have never smoked (Table 5.1). Participants with a history of significant cricket-related hand injury reported playing a higher number of cricket seasons and playing at a higher standard compared to those without a history of significant cricket-related hand injury (Table 5.1).

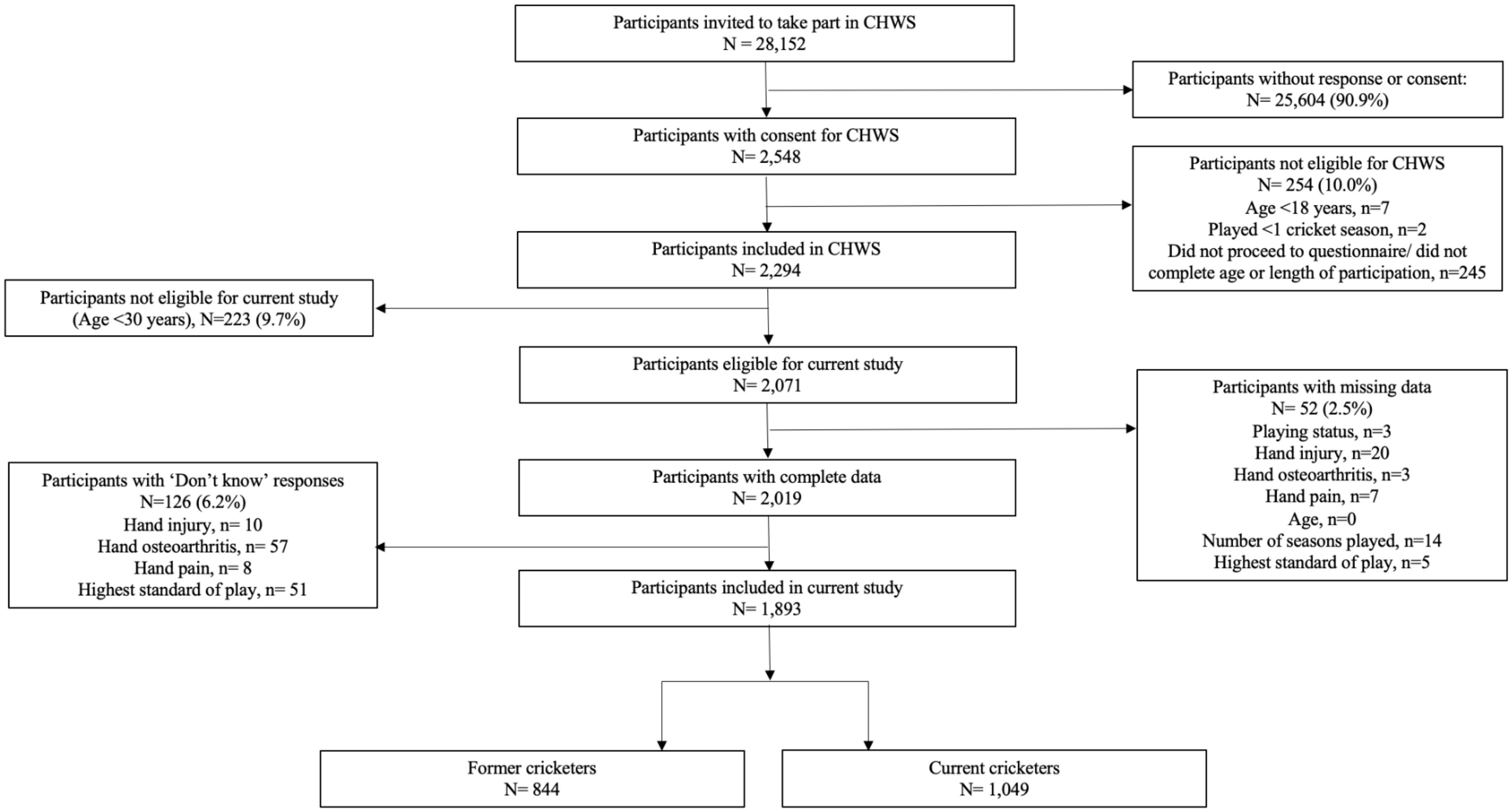

Figure 5.4: Flowchart of participants included in the current study

CHWS: Cricket Health and Wellbeing Study

Table 5.1: Demographics of all participants, those with, and those without a history of self-reported significant cricket-related hand injury

	All participants N= 1,893	Hand injury n= 315 (16.6%)	No hand injury n= 1578 (83.4%)
Sex:			
Male [N(%)]	1838 (97.1)	309 (98.1)	1529 (96.9)
Female [N(%)]	43 (2.3)	3 (1.0)	40 (2.5)
Other [N(%)]	1 (0.1)	0	1 (0.1)
Do not wish to disclose [N(%)]	1 (0.01)	0	1 (0.1)
Missing data [N(%)]	10 (0.5)	3 (1.0)	7 (0.4)
Age (years) Mean (SD):	54.7 (12.1)	53.9 (12.0)	54.9 (12.2)
BMI (kg/m^2) Mean (SD):	28.0 (4.8)	27.9 (4.7)	28.1 (4.8)
Smoking status:			
Current [N(%)]	141 (7.4)	24 (7.6)	117 (7.4)
Former [N(%)]	317 (16.7)	63 (20.0)	254 (16.1)
Never smoked [N(%)]	1427 (75.4)	225 (71.4)	1202 (76.2)
Missing [N(%)]	8 (0.4)	3 (1.0)	5 (0.3)
Ethnicity:			
Caucasian [N(%)]	1733 (91.5)	291 (92.4)	1442 (91.4)
Non-Caucasian [N(%)]	193 (10.2)	21 (6.7)	118 (7.5)
Do not wish to disclose [N(%)]	16 (0.8)	2 (0.6)	14 (0.9)
Missing [N(%)]	5 (0.3)	1 (0.3)	4 (0.3)
Number of seasons played Mean (SD):	30.8 (14.4)	34.2 (12.4)	30.1 (14.7)
Highest standard of play:			
Higher (International/ County/ Premiere league/ Academy/ County-age-group) [N(%)]	703 (37.1)	138 (43.8)	565 (35.8)
Lower (University/ School/ Village/ Social) [N(%)]	1190 (62.9)	177 (56.2)	1013 (64.2)

BMI: Body mass index; SD: Standard deviation
Hand injury relates to a self-reported history of significant cricket-related hand injury

5.4.3.2 Association between a history of cricket-related hand injury and hand osteoarthritis

A history of significant cricket-related hand injury was reported in 630 hands, with ipsilateral osteoarthritis reported in 38 (6.0%) of these hands (frequency table shown in Appendix 5.7). A history of significant cricket-related hand injury was associated with a 2.6 times (95% CI: 1.7 to 3.8) increased odds of ipsilateral hand osteoarthritis (Table 5.2). This relationship remained after adjustment for age, length of participation and playing standard (OR: 3.1, 95% CI: 2.1 to 4.7) (Table 5.2).

Subgroup analysis

a) Dominant hand

In the subgroup analysis for the dominant hand, a history of significant cricket-related hand injury was reported in 247 dominant hands, with ipsilateral hand osteoarthritis reported in 18 (7.3%) of these hands (frequency table shown in Appendix 5.7). A history of significant cricket-related hand injury in the dominant hand was associated with a greater odds of hand osteoarthritis in the dominant hand (OR: 2.2, 95% CI: 1.3 to 3.9), even after adjusting for confounders (OR: 2.7, 95% CI: 1.5 to 4.9) (Table 5.2).

b) Non-dominant hand

In the subgroup analysis for the non-dominant hand, a history of significant cricket-related hand injury was reported in 228 non-dominant hands, with ipsilateral hand osteoarthritis reported in 14 (6.1%) of these hands (frequency table shown in Appendix 5.7). A history of significant cricket-related hand injury in the non-dominant hand was associated with a greater odds of hand osteoarthritis in the non-dominant hand (OR: 2.6, 95% CI: 1.4 to 4.9), even after adjusting for confounders (OR: 3.2, 95% CI 1.7 to 6.1) (Table 5.2).

5.4.3.3 Association between a history of cricket-related hand injury and chronic hand pain

In former cricketers, a history of significant cricket-related hand injury was reported in 244 hands, with ipsilateral chronic hand pain reported in 34 (13.9%) of these hands (frequency table shown in Appendix 5.6). A history of significant cricket-related hand injury was associated with a 2.3 increased odds (95% CI: 1.5 to 3.6) of ipsilateral chronic hand pain. This relationship remained following adjustment for age, length of participation and playing standard (OR: 2.2, 95% CI: 1.4 to 3.6) (Table 5.2).

Subgroup analysis

a) Dominant hand

In the subgroup analysis for the dominant hand, a history of significant cricket-related hand injury was reported in 90 dominant hands, with ipsilateral chronic hand pain reported in 14 (15.6%) of these hands (frequency table shown in Appendix 5.7). A history of significant cricket-related hand injury in the dominant hand was associated with a greater odds of chronic hand pain in the dominant hand (OR: 2.1, 95% CI: 1.1 to 3.9), even after adjusting for confounders (OR: 2.0, 95% CI: 1.0 to 3.9) (Table 5.2).

b) Non-dominant hand

In the subgroup analysis for the non-dominant hand, a history of significant cricket-related hand injury was reported in 83 non-dominant hands, with ipsilateral chronic hand pain reported in 11 (13.3%) of these hands (frequency table shown in Appendix 5.7). A history of significant cricket-related hand injury in the non-dominant hand was also associated with a greater odds of chronic hand pain in the non-dominant hand (OR: 2.2, 95% CI: 1.1 to 4.4), even after adjusting for confounders (OR: 2.2, 95% CI 1.0 to 4.4) (Table 5.2).

Table 5.2: Association between a history of significant cricket-related hand injury with hand osteoarthritis and chronic hand pain

		Ipsilateral Hand Osteoarthritis		Ipsilateral Chronic Hand Pain	
		OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
All hands	Hand injury	2.6 (1.7 to 3.8)	p<0.001	2.3 (1.5 to 3.6)	p<0.001
	Hand injury adjusted for age	2.8 (1.9 to 4.2)	p<0.001	2.3 (1.5 to 3.6)	p<0.001
	Hand injury adjusted for age, length of cricket participation	3.2 (2.1 to 4.8)	p<0.001	2.4 (1.5 to 3.9)	p<0.001
	Hand injury adjusted for age, length of cricket participation, playing standard	3.1 (2.1 to 4.7)	p<0.001	2.2 (1.4 to 3.6)	p=0.001
Dominant hand	Hand injury	2.2 (1.3 to 3.9)	p=0.004	2.1 (1.1 to 3.9)	p=0.024
	Hand injury adjusted for age	2.5 (1.4 to 4.4)	p=0.001	2.1 (1.1 to 4.0)	p=0.023
	Hand injury adjusted for age, length of cricket participation	2.8 (1.6 to 5.0)	p=0.001	2.2 (1.6 to 4.3)	p=0.016
	Hand injury adjusted for age, length of cricket participation, playing standard	2.7 (1.5 to 4.9)	p=0.001	2.0 (1.0 to 3.9)	p=0.046
Non-dominant hand	Hand injury	2.6 (1.4 to 4.9)	p=0.003	2.2 (1.1 to 4.4)	p=0.028
	Hand injury adjusted for age	2.8 (1.5 to 5.3)	p=0.001	2.2 (1.1 to 4.4)	p=0.031
	Hand injury adjusted for age, length of cricket participation	3.2 (1.7 to 6.1)	p<0.001	2.2 (1.1 to 4.6)	p=0.028
	Hand injury adjusted for age, length of cricket participation, playing standard	3.2 (1.7 to 6.1)	p=0.001	2.2 (1.0 to 4.4)	p=0.039

95% CI: 95% Confidence interval; OR: Odds ratio. All analyses were performed on the hand level.
Hand osteoarthritis was assessed in current and former cricketers. Hand pain was assessed in former cricketers only.
Dominant hand was the hand used to bowl or throw

5.4.4 Discussion

5.4.4.1 Summary

A history of significant cricket-related hand injury increased the odds of ipsilateral hand osteoarthritis in cricketers, and increased the odds of ipsilateral chronic hand pain in former cricketers. These associations were seen in all hands, and also in subgroup analyses for the dominant and non-dominant hands separately. The current study suggests the association between a history of significant cricket-related hand injury with hand osteoarthritis and chronic hand pain cannot be explained by age, number of seasons played, or standards of playing.

The current study found a 3.2 times increased odds of hand osteoarthritis in cricketers with a history of significant cricket-related hand injury. These results are different to a recent study of retired elite male cricketers and rugby players that found no association between hand injury and pain and osteoarthritis in either type of athletes (353). However, that study had a small sample size of 127 cricket players, and only recruited retired cricket players from the Professional Cricketers' Association. They also combined the data from cricketers with data from 140 rugby players. Injuries in professional rugby players most commonly occur to the lower limb and shoulders, and are less common in the hands or fingers, and indeed, the prevalence of hand injuries in that study was lower in rugby players compared to cricket players (354). In the current study, a larger sample size of cricketers was included, which should increase precision of the effect outcome, and the higher prevalence of hand osteoarthritis is also more likely to have detected an association if one exists.

An increased exposure to playing cricket might also increase the load through the joints. To better understand the role of repetitive loading through the hand joints and its relationship with hand osteoarthritis, the current study performed subgroup analyses for the dominant and non-dominant hands separately. The dominant hand identified whilst playing cricket is more likely to experience repetitive loading through the hand joints. Repetitive joint loading is thought to cause microtrauma at the joint site (355). In the hands, initial studies on hand osteoarthritis investigated cotton weavers and spinners, and reported these workers as having an increased risk of hand osteoarthritis, thought to be due to repetitive joint loading through their work (283). In the current study, the results found that there was a 2.7 times increased odds of hand osteoarthritis in the dominant hand in cricket players with a history of significant cricket-related injury in the ipsilateral hand. These results add to the body of literature providing evidence for an association between repetitive joint loading at the hands with hand osteoarthritis.

The relationship between acute traumatic hand injury and hand osteoarthritis was investigated in the sub-group analysis in the non-dominant hand. The non-dominant hand is used by cricketers when catching the ball with two hands, and when batting. As it is less frequently used than the dominant hand, it might be expected to have less strength and proprioception, increasing the risk of acute injury. In the first study of this chapter, the prevalence of severe hand injury (presenting to hospitals) in cricket players was found to be 34.2 out of 10,000 cricketer years. Hand injuries were most commonly caused by being hit by the ball, and were most commonly fractures. Acute traumatic injury is often considered a risk factor for osteoarthritis in the lower limbs, and the systematic review (Chapter 2) found that a history of finger fracture is known to be a risk factor for incident IPJ osteoarthritis (148, 167). The results from the current study found a 3.2 times increased odds of hand osteoarthritis in the non-dominant hand in cricket players with a history of significant cricket-related injury in the ipsilateral hand. This suggests that injuries sustained in the non-dominant hand, which might be more likely to be acute traumatic injuries such as fractures, increase the risk of future hand osteoarthritis.

In the current study, chronic pain was the secondary outcome measure, and used as a marker of osteoarthritis. Pain has been used as a marker of osteoarthritis in the knee and hip. And, in studies of hand osteoarthritis involving patients, such as randomised controlled trials, pain is commonly used as a marker of hand osteoarthritis (115). However, pain from hand osteoarthritis can be difficult to quantify, and is often measured with other symptoms, such as stiffness in the ACR criteria for hand osteoarthritis, or with loss of function in patient reported questionnaires. In studies of lower limb osteoarthritis, the NHANES criteria is often used to capture pain from osteoarthritis (97, 98). In the current study, the NHANES criteria was used to capture chronic hand pain in former cricketers, to prevent confounding from acute hand pain in current cricketers (mostly likely caused by acute hand injury). In the current study, similar associations were found between both a history of significant cricket-related hand injury and chronic hand pain, and a history of significant cricket-related hand injury and osteoarthritis. This suggests that using the NHANES criteria to capture chronic hand pain might be a good marker for hand osteoarthritis. Acute cricket-related hand injuries could lead to acute hand pain. As this study aimed to assess the relationship between hand injury and chronic pain (as a marker of osteoarthritis), current cricketers were excluded from the analysis of hand pain, to prevent the effect of acute hand injury. Indeed, the prevalence of hand injury was higher in current cricketers compared to former cricketers. Interestingly, the prevalence of hand pain was lower in current cricketers compared to former cricketers, suggesting that the NHANES pain question does not capture acute pain, perhaps as it identified pain over a period of one month.

In former cricketers in the CHWS, the hands are the third most prevalent site with chronic pain (following the knee and the back) (356). The high prevalence of chronic hand pain is concerning, as hand pain due to osteoarthritis is known to be severe, with effects on both the physical and mental health of patients (34). Within former cricketers in the CHWS, persistent upper extremity pain has been shown to be associated with worse physical component scores, exceeding the minimal clinically important difference, and this is likely to include pain from hands (357). Preventing both hand osteoarthritis and chronic hand pain in cricket players could be initially addressed by preventing significant cricket-related hand injury.

5.4.4.2 Potential limitations

Limitations with study population

The entire population of cricketers, across England and Wales, who consented to be contacted for research and were eligible for the CHWS, were sent the CHWS questionnaire. However, over 90% did not respond. It is possible there was non-response bias in cricketers who did not respond or did not consent to joining the CHWS. However, it was not possible to capture the demographics of participants who did not respond to the CHWS questionnaire as they did not provide any further data, and consent was not in place to analyse their data from the EWCB database. It is possible that participants might not have responded if they were unable to use an online questionnaire, which itself could be due to older age or less familiarity of using electronic tools. As age is known to be a risk factor for incident hand osteoarthritis (Chapters 2 and 3) (26), if older cricket players did not consent to joining the CHWS it is possible that a lower prevalence of hand osteoarthritis might be reported in the CHWS participants. However, to prevent the effect of age on the current study, age was adjusted for in the analysis, and the result remained significant.

Limitations with data collection and variables

The data collection tool used in the CHWS was a self-reported questionnaire. Self-reported data could capture information not reported in healthcare records, particularly if records are incomplete (290). However, in a systematic review of self-reported data for the use of healthcare services (290), self-reported data has been found to vary in accuracy. The accuracy has been shown to decrease as patients are asked to recall longer periods, resulting in more under-estimation of events (290). Participants in the study were of mean age 50.2 years. The study assessed a history of significant cricket-related hand injury. However, the time of hand injury is not known, though it is possible this could be many years in the past. Therefore, it is possible that the prevalence of hand injury could be under-represented in the study, resulting in a bias towards the null.

The type and number of cricket-related hand injuries was not described by the cricketers. From the first study in this chapter, it is clear that fractures and dislocations are the most prevalent injuries requiring hospital treatment. However, a large proportion (between 20% to 50%) of cricket-related injuries were either superficial injuries, open wounds, or unspecified injuries, which are considered to be less likely to be associated the development of hand pain and osteoarthritis in the future, as the chance of them communicating with the joint is low. If cricketers in this study sustained a high number of fractures, this may account for the development of osteoarthritis, as the systematic review of risk factors for incident IPJ osteoarthritis found a history of finger fracture was a risk factor for IPJ osteoarthritis (Chapter 2).

In the first study in this chapter, 34.2 out of 10,000 cricketers sought hospital treatment for hand injury. However, in this second study, it is also not possible to know whether the cricket-related hand injuries received any treatment. Elite cricketers might have been more likely to receive treatment either at the side of the pitch from team doctors, or in a healthcare setting compared to recreational cricketers. Athletes also commonly receive additional investigations, closer monitoring, and extensive management during their playing career (358). This should facilitate rehabilitation of injuries, and could decrease the chance of long-term sequalae, such as osteoarthritis in elite cricketers. In our study, over one third of cricketers identified as playing at higher standard. To account for those playing at higher standard and the possible difference in injury management, the analysis was adjusted for playing standard in the stepwise regression. Following this adjustment, there was a small decrease in the odds of hand pain and hand osteoarthritis, suggesting playing standard might be a confounder for hand injury and hand pain / osteoarthritis, though the overall result remained significant.

The secondary outcome measure in the current study was chronic hand pain. There is currently no established criteria to measure the frequency or severity of hand pain arising from hand osteoarthritis (359). Hand pain from osteoarthritis also varies over time, showing a daily diurnal pattern (33). Pain from osteoarthritis at one hand joint can also radiate, presenting as referred pain in a different hand joint, such that the presenting anatomical location of pain does not correlate with the anatomical location of osteoarthritis (360). For pain in hand osteoarthritis, it is often measured through questionnaires addressing loss of hand function (detailed in Chapter 1), but in these questionnaires, hand pain cannot be extracted from other questions. For the knee and hip osteoarthritis, asking about pain on 'most days in the last month' is one of the most commonly used types of the NHANES questions (97). This type of NHANES pain question was used to assess hand pain from osteoarthritis in the CHWS. The prevalence of pain can vary depending on the type of NHANES pain question (97). Assessing pain on 'most days in the last month' has been found to have the high specificity but low sensitivity for radiographic knee osteoarthritis (361). As such, it is possible that using this type of NHANES pain question might underrepresent the prevalence of pain and, possible osteoarthritis. Further work is needed to more accurately characterise pain from hand osteoarthritis, particularly if using different versions of the NHANES pain questionnaire, and take into account referred pain from different hand joints. This could include an examination of joints for tenderness, though this would require participants to present themselves for a clinical assessment.

Hand osteoarthritis was captured using a self-reported doctor diagnosis. In addition to the above-mentioned limitations of using a self-reported questionnaire, it is also unclear whether participants were diagnosed with osteoarthritis based on symptoms or radiology. The prevalence of radiographic hand osteoarthritis is more than three times higher than that of symptomatic hand osteoarthritis (362). Participants who presented to a primary care doctor might be more likely to be diagnosed based on symptoms, whilst those in tertiary or specialist care might be more likely to have radiographs, or other radiological investigations, performed. This study should have captured this entire spectrum of hand osteoarthritis presentations presenting to doctors. The health-seeking behaviour of cricketers has also not yet been described in the literature. Though, in the general population, the prevalence of men aged 45 to 64 years seeking treatment for hand osteoarthritis from GPs is 3% (185). In this study, 4.3% of cricketers reported a doctor diagnosis of hand osteoarthritis. This could suggest that the prevalence of hand osteoarthritis in cricketers is higher than in the general population, but this could also be due to health-seeking behaviours of cricketers, including seeking treatment from specialist doctors.

Limitations with statistical analysis

In the current study, a cross-sectional analysis was to assess the relationship between a history of significant cricket-related hand injury and chronic hand pain and hand osteoarthritis, and therefore cannot be used to infer a causal relationship. Additional other factors unaccounted for in the CHWS might have influenced the observed results. For example, grip strength is thought to be a risk factor for hand osteoarthritis (across all joints) and a 'power' style grip used when holding a stick or bat (363), such as when batting in cricket, exerts high compression forces across the IPJs and the first CMCJ (364, 365) which might be associated with hand osteoarthritis. As grip strength is not measured in the CHWS, it was not possible to account for it in the analysis.

The subgroup analysis assessed the dominant and non-dominant hands separately. In this study, the dominant hand is considered to represent repetitive injury, whilst the non-dominant hand is considered to represent acute injury. However, repetitive and acute injuries do not exclusively occur in the dominant and non-dominant hands respectively. Therefore, there could be mis-classification regarding the nature of injury, based on which hand a study participant reported injury in.

5.4.4.3 Strengths

This is the largest study to date to assess the relationship between cricket-related hand injuries with pain and osteoarthritis. It includes both elite and recreational cricket players, and male and female players. Cricketers were also captured from across England and Wales, allowing for a large group of players to be assessed. Age was found to be an important risk factor for the incidence of

IPJ osteoarthritis in both the systematic review (Chapter 2) and the prediction model (Chapter 3). This analysis accounts for age in the stepwise logistic regression. Similarly, the odds of hand pain also have been reported as higher in former cricketers playing at higher standard compared to those playing at lower standard in the CHWS (356), and to account for standard of play, both length of cricket participation and playing standard were adjusted for in this analysis.

5.4.4.4 Translating research to clinical practise for both studies

Both studies in this chapter are some of the first studies to assess a) the type, nature, and severity of hand injury in cricketers, and b) the association between a history of significant cricket-related hand injury with hand osteoarthritis and chronic pain. They provide some insight into the types of injuries and sequalae of these injuries which we might expect to see in patients who are/were cricketers.

Within cricket-related hand injuries presenting to hospital, sex and age differences were seen across the results. Both players most commonly injured the thumb and little finger, and women most commonly attended to EDs with dislocations, but were most commonly admitted to hospitals for fracture. Their injuries most commonly occurred due to being hit by the ball, but in those who were admitted, falling injuries were also high. As such, there should be increased clinical awareness of these presentations, differing by sex.

Children most often injured their thumb, resulting in fractures and dislocations most commonly. Dislocations could be managed in the ED, but fractures and open wounds needed admission. In children, being hit by the ball frequently caused injuries, but there was also a high prevalence of falls. In older players, the little finger was most often injured, resulting in fractures and dislocations. Open wounds were also common, but treated in EDs, whilst muscle injuries were common and required admission. The majority of injuries in older players were due to falls. These results indicate that children with open hand wounds and older players with muscle injuries can be expected to be admitted to hospital for further treatment, and that only ED management might not be sufficient. In both age spectrums, injuries due to falls can be expected, and are likely to require admission.

The increased odds of hand osteoarthritis and chronic hand pain highlight the need for hand-injury prevention programmes in cricket. These should be targeted by sex and age, due to the differences in causes and types of injuries across these groups. Such prevention strategies could include the use of personal protective equipment, such as gloves. The odds of hand/finger injuries and fractures have been shown to be significantly higher in athletes not using gloves, compared to those using gloves, in stick-handling sports (366). Within cricket, gloves are only permitted to be worn by batsmen and wicketkeepers. Increasing the use of wearing gloves, is likely to require a change in the nature of playing cricket, and therefore would need policy review before it is considered. Additionally, falls prevention should be prioritised in females, children, and older players. This could be through kinematic training, to both prevent the incidence of falls, and to decrease the impact experienced during falls. This could be implemented during training regimes, and can be incorporated as part of the guidelines of playing cricket. If preventative measures, such as the use of personal protective equipment and kinematic training are implemented, their effectiveness should then be evaluated (334).

5.5 Future research

This study has described the immediate results of cricket-related hand injuries, including hospital admission, and the longer-term consequences of injury, such as persistent hand pain and hand osteoarthritis. Further work should aim to develop both preventative and rehabilitation training regimes, including physiotherapy, and be evaluated using prospective randomised controlled trials. Future research should also investigate the causal relationship between cricket-related hand injury and osteoarthritis, using a prospective parallel cohort design.

6 CHAPTER 6: CONCLUSION

6.1 Main Findings and Clinical Implications

This thesis aimed to develop a better understand of risk factors for development of, and prognostic factors for progression of, hand IPJ osteoarthritis.

In Chapter 2, systematic reviews and Delphi studies were performed to identify risk factors for the presence of IPJ osteoarthritis, and prognostic factors for the progression of IPJ osteoarthritis. The first systematic review found that female sex and older age in women are risk factors for the presence of IPJ osteoarthritis, and that age, family history of hand osteoarthritis in mother, and direct injury to the joint are all important risk factors hand surgeons identify in their patients in clinic (148, 348). There were no prognostic factors for the progression of IPJ osteoarthritis with strong or moderate evidence in the literature, though the Delphi study reported age, and family history of hand osteoarthritis in mother, brother, and father as prognostic factors in patients presenting to hand surgery clinics (147, 348). In the systematic reviews, most risk factors were assessed using univariable analyses. Using multivariable analysis with multiple potential risk or prognostic factors, such as in a prediction or prognostic model, would allow the overall risk of both incident IPJ osteoarthritis and its progression to be calculated (142), and this was performed in Chapters 3 and 4.

In Chapter 3, a prediction model using logistic regression was developed to predict the risk of incident radiographic IPJ osteoarthritis. The model found that older age, manual occupation, and radiographic first CMCJ osteoarthritis are important risk factors. In particular, manual occupation is a modifiable risk factor which could be changed to decrease the risk of an individual person developing IPJ osteoarthritis in the future. The relationship between first CMCJ and IPJ osteoarthritis also suggest that osteoarthritis at these sites might either be a continuum of one disease process, instead of different subsets or different phenotypes. Alternatively, in a patient with first CMCJ osteoarthritis, the resulting change in the biomechanics and loading across the hand joints might lead to IPJ osteoarthritis. The model was internally validated, and the performance showed a c-statistic of 0.66 and a calibration slope of 1.12, demonstrating acceptable discrimination, below the 0.7 threshold often used to describe a model with good discrimination. The model was mis-calibrated, suggesting underfitting of the data. In the future, the model might be improved by increasing the sample size.

In Chapter 4, a prognostic model using proportional odds logistic regression for the progression of radiographic IPJ osteoarthritis was developed. Few studies in the literature have developed a prognostic model using this methodology, and this is considered to be a novel technique in the way it combines the statistical methodology of both proportional odds logistic regression and prognostic modelling. The model was initially developed in the Chingford Study, but no prognostic factors were found to be important for the progression of radiographic IPJ osteoarthritis. The model performance was poor (c-statistic of 0.57 and calibration slope of the middle outcome level of 1.38). When externally validated and re-calibrated in the JoCo Project (in women only), the model's performance still remained poor, suggesting it is not transportable to a similar population, and not appropriate for use in clinical practice. When the model was assessed separately in the geographical subgroups, the performance improved, suggesting that using the broad primary outcome definition was one cause for poor model performance.

The model was then re-developed in the JoCo Project in both men and women, and female sex was found to be an important prognostic factor. Though the systematic review reported in chapter 2 found that prior literature assessing the role of gender and sex as a prognostic factor for radiographic IPJ osteoarthritis progression is lacking, it did find that female sex is a risk factor for incident radiographic IPJ osteoarthritis (147, 148). This suggests that overall women are both more likely to develop radiographic IPJ osteoarthritis (from the systematic review in Chapter 2), and more likely to have progressive disease (from the prognostic model in Chapter 4), compared to men. As the model suggests that female sex is an important risk factor for radiographic IPJ osteoarthritis progression, it would be prudent to consider targeting women in the first instance for preventative strategies.

In Chapter 5, the role of hand injury and its association with hand osteoarthritis was further investigated. Populations of cricket players were used to address this question, as the incidence of hand injury in sports players, particularly in those using a ball and stick such as cricketers, is known to be high. My first study reported a decreasing incidence of hand injuries presenting to public hospitals in Victoria, Australia between 2007/8 and 2017/18. Those cricketers presenting to EDs only were most commonly aged between 13 and 34 years, most commonly presented with fractures or dislocations, and hand injuries were most often due to being hit by the ball. Cricketers with hand injuries requiring hospital admission were most commonly aged 25 to 34 years, required treatment for fractures, and injuries were again most often due to being hit by the ball, though in patients ≤12 years and ≥55 years, injuries due to falls were also common. These results indicate that clinicians can expect that cricketers who require hospital treatment are most likely to be young adults with fractures. These injuries are likely to necessitate admission for further management, though these inpatient stays are likely to be for <2 days, suggesting they can be appropriately managed in day-case or ambulatory settings.

In my second study in Chapter 5, the relationship between hand injury and osteoarthritis was assessed, as previous trauma was suggested by clinicians to be an important factor predisposing to IPJ osteoarthritis in the Delphi study (Chapter 2), but could not be well assessed in the prediction model (Chapters 3), likely due to low prevalence. In cricket players with a history of significant hand injury, the odds of both hand osteoarthritis and hand pain were increased more than two-fold (367). The associations between hand injury and both osteoarthritis and pain remained in subgroup analyses of both the dominant and non-dominant hand, suggesting that injuries caused by either acute trauma (hypothesised to be more likely in the non-dominant hand) and repetitive microtrauma (hypothesised to be more likely in the dominant hand) are both likely to play important roles in the pathogenesis of hand osteoarthritis (367). The prevalence of chronic pain in former cricketers was also higher than that observed in the general UK population, highlighting hand osteoarthritis may be causing this high prevalence of pain (368).

6.2 Important Limitations

The main limitation of both systematic reviews was the high risk of bias studies identified in the literature. The reviews themselves were also limited by the lack of meta-analysis. In particular, there was no consensus criteria used for the diagnosis of either the presence of, or progression of, IPJ osteoarthritis, despite all studies assessing osteoarthritis radiographically. This heterogeneity made it difficult to pool data across studies, and increased the uncertainty of results.

The Delphi studies were mainly limited by the small response rate from hand surgeons, and the high attrition across rounds. Though the literature has shown that Delphi panel members are likely to be representative of their peers, it is possible that due to this small response and high attrition rate, the Delphi studies have not captured the breadth of possible responses from hand surgeons across the UK (193).

Both the prediction and prognostic models were developed using logistic regression, as there was no time to event data available. Therefore, it was not possible to establish when the onset of radiographic IPJ osteoarthritis began, and what the rate of progression was. Therefore, these models can only be used to determine the presence or progression of IPJ osteoarthritis at 10 years, and not to predict when these changes will occur. This means we cannot differentiate between rapid and slower progressors. The lack of time to event data may have also reduced the number of important predictors identified by the model, as a greater proportion of participants would develop the outcome over a prolonged time period (and this would be a combination of rapid progressors, slow progressors, and age-related changes).

Both models were also limited by power, and in particular the $R^2_{Nagelkerke}$ for the model for incident IPJ osteoarthritis was 0.02, and with 18 candidate predictors, the optimum model should have 8,010 participants with 3,526 events, suggesting the model was underpowered. Sample size calculations have not yet been developed for proportional odds logistic regression, and it is likely the prognostic model for the progression of IPJ osteoarthritis was also underpowered, due to the small number of participants. Future research should focus on developing sample size calculations for proportional odds logistic regression prognostic models, which can be used to inform such models.

It was also not possible to assess how changes in modifiable risk factors, such as changes in smoking habits or changes in occupation, might affect the outcomes, as risk factors were only assessed at baseline. Any change in modifiable risk factors over the 10-year follow-up period is likely to weaken the association of the risk factor with the outcome, and therefore decrease the power of the model. Future models should utilise data on changes in predictors over time, though methodology for this is lacking

In addition, the outcomes for both models used radiographic osteoarthritis, and were not able to assess osteoarthritis based on symptoms or signs. As the relationship between radiographic and symptomatic hand osteoarthritis is not well correlated, it is possible that risk factors or prognostic factors for symptomatic IPJ osteoarthritis might be different to those identified from the models. The model for incident IPJ osteoarthritis was not externally validated.

The model should be externally validated, which would also enable testing of its generalisability in similar populations recruited at different sites or at different times (261). However, this is currently not possible, as there is no other longitudinal population-based cohort study which has captured similar baseline variables to those in the Chingford Study.

The study assessing the incidence, pattern and severity of hand injury in cricketers, was limited by the inherent nature of routinely collected data. Specifically, this study was undertaken using a secondary analysis of data collected from the VISU. A validation study of injury data in the VEMD, a database held by VISU, has reported at least one error in 87% of records, and, therefore, there may have been misclassification of some of the data in this study (351). If the misclassification was random, it is unlikely to have a major effect on the results. If the misclassification was non-random, in the important variables of type of injury and cause of injury, this could have caused false positive results in the study. Previous literature has shown that 90% validity for data concerning the nature (type) of injury, it is unlikely that any misclassification was non-random or in the important outcome variables, though this could not be directly assessed (351). Additionally, this study only used data collected from patients presenting to hospital, and those treated outside of hospital, such as on the field or in the community by GPs or physiotherapists, have not been captured. This means the incidence of hand injury in cricketers is likely to be underreported in this study. Conversely, I have analysed data on more significant hand injuries, which are likely to be of more consequence both to the patient, immediately and in the longer term.

In the second study, the number of hand injuries were compared to the number of cricketers, allowing an incidence rate to be calculated. However, data on the number of cricketers stratified by sex and age was not available, and therefore absolute numbers for the pattern and severity of injuries were reported. As a larger number of males compared to females play cricket, the results of my study reflect this, with a large proportion of male compared to female patients requiring hospital treatment. Extrapolation of the results to female cricketers should proceed with caution.

Finally, the study assessing the relationship between hand injury and osteoarthritis and pain in cricketers from the EWCB, was based on a secondary analysis of data from the CHWS. The

CHWS is a cross-sectional study, and therefore the temporal relationship between a history of hand injury and the onset of hand osteoarthritis and pain is not known. The study is only able to provide insight into an association, and not causation. Data was also collected using a self-reported questionnaire. Self-reported data are likely to vary in accuracy, and accuracy is known to decrease when recall periods are prolonged, such as in retired cricketers who might have experienced hand injuries when playing cricket a long time ago (290). Therefore, it is possible the prevalence of hand injury in this study might have been under reported. Hand osteoarthritis was also captured using a self-reported doctor diagnosis. It was unclear whether this would capture both the radiographic and clinical burden of hand osteoarthritis, and currently there are no validation studies assessing the accuracy of the self-reported questionnaires with healthcare records in the EWCB. There was also a lack of granularity to the data, such that IPJ and first CMCJ osteoarthritis could not be assessed separately. Though Chapter 3 found that first CMCJ radiographic osteoarthritis is an important risk factor for incident radiographic IPJ osteoarthritis, it was not possible to assess these as separate outcomes using the CHWS data.

6.3 Future Research

The systematic reviews found no consensus in the classification criteria for either the presence of, or the progression of, IPJ osteoarthritis. Future work should focus on developing consensus criteria, which can be reproduced in multiple studies. For clinical trials of drugs in hand osteoarthritis, working groups have published guidelines stating that hand osteoarthritis should be defined using the ACR criteria, and that affected joints should be KL grades 2 or 3 at baseline (116). This means that patients need to have both radiographic and symptomatic features of hand osteoarthritis. Similar guidelines for epidemiological studies have not yet been developed. As capturing the symptoms and/or clinical signs from osteoarthritis is likely to have large variability across patients, the first step might instead be to develop consensus radiographic criteria. This would allow the pooling and meta-analysis of data across multiple established prospective cohort studies of hand osteoarthritis. The first step towards establishing consensus will be performed at the OARSI 2021 Congress, through a Working Group which I will chair, whereby attendees will vote on and discuss the importance of phenotypes in hand and IPJ osteoarthritis. The prognostic model for the progression of IPJ osteoarthritis also found that the model performance improved when geographical and local progression were assessed separately. This suggests consensus criteria for IPJ osteoarthritis progression should take into account the patterns of osteoarthritis spread across hand joints.

The prediction model and the prognostic model are the first of their kind to assess multiple risk factors for incident, and progression of, radiographic IPJ osteoarthritis. The prediction model for incident IPJ osteoarthritis should be externally validated before it is considered for use clinically. The performance measures of the models also suggest there are other potential risk factors which were not included in the models but might affect the risk of the outcome. In particular, few localised risk factors were included as candidate predictors in the model. Hand fracture was found not to be an important risk factor for the incidence of radiographic IPJ osteoarthritis, through hand injury was associated with doctor diagnosed hand osteoarthritis in the CHWS. This is likely to be because the prevalence of hand fracture was too low in the Chingford Study to be accurately modelled. Future prediction models should consider the importance of hand injuries and fractures in populations where the prevalence is higher. The models also did not include genetic risk factors, though a family history of hand osteoarthritis was included as a candidate predictor. To better understand the role of genetics and whether there are particular associations for incident, and progression of radiographic IPJ osteoarthritis, well-designed genome-wide association studies are required. Such studies would need a large biobank with linked hand radiographs taken at intervals over time. Currently, well-established population-based biobanks such as UK Biobank do not have this richness of phenotypic data. However, a straightforward genome wide association study and replication study looking at severe hand osteoarthritis (combining both first CMCJ and IPJ osteoarthritis) has been reported (369). This study discovered two significant loci associated with hand osteoarthritis, and the replication cohorts included data from 578 women in the Chingford study.

Newer cohorts assessing hand osteoarthritis would benefit from taking repeat radiographs more frequently, to monitor the onset and progression of disease. In addition, studies would also benefit from collecting data on the symptoms and signs of hand osteoarthritis, such as pain and loss of function, to assess risk factors for incident symptomatic hand osteoarthritis. This might allow the identification of different phenotypes of hand osteoarthritis, such as the erosive and inflammatory phenotypes which may not often be visible on plain film radiographs, and a better understanding of their risk factors. Clinical examinations of the hands of participants have been performed in the Chingford Study one year from baseline, assessing for tenderness and swelling. However, similar repeat examinations have not been performed at other time periods. Instead, at 19 years from baseline, the presence of nodes (DIPJ osteophytes) has been assessed. If there were multiple reproducible clinical examinations, it may be possible to attempt to develop a prediction model for incident clinical osteoarthritis in the Chingford Study.

The clinical utility of the prediction model for incident radiographic IPJ osteoarthritis also needs to be assessed using real world data. Currently, no data exists to determine the clinical threshold at which people presenting to healthcare are considered to be at risk of developing IPJ or hand osteoarthritis. If this data is captured, it can be used to inform and update the decision curve analysis, to better understand at which thresholds the prediction model might be useful. The actual clinical utility of the model has also not been assessed and it is recommended to test the impact of a prediction model through cluster-randomised trials (370). Before this can be done, the model should be externally validated, and then re-calibrated for the new setting in which it will be tested. This is not currently possible for the prediction model for incident radiographic IPJ osteoarthritis, as there are no external datasets with similar variables available. To test the model using a trial design, the model should be used in the 'intervention' arm, to identify patients at highest risk of the outcome, and if appropriate, to guide management decisions (370). In the control arm, 'care-as-usual' (i.e. without the prediction model) should be performed (370). However, running a cluster-randomised trial requires a large sample size, limiting the use of this study design. Instead, a non-randomised interrupted time-series study could be used. In this situation, the model could be used for a predetermined period of time, and the outcomes compared to another pre-determined period of time when the model is not used. Though, testing the model using either a cluster-randomised trial or an interrupted time-series study might still be difficult for the nomogram from the prediction model for incident radiographic IPJ osteoarthritis, as the outcome (radiographic IPJ osteoarthritis) is measured 10 years later, and will require a prolonged follow up time.

The results from both cricket studies suggest that the prevalence of hand injury in cricketers, severe enough to require hospital assessment and sometimes inpatient treatment, is high. The long-term effects of hand injury include hand osteoarthritis and a sequalae of that seems to be chronic hand pain, as may be expected. In order to prevent hand osteoarthritis and pain in cricketers, strategies to prevent injury need to be tested and implemented (333, 334). These might include personal protective equipment, such as gloves, or kinematic training to prevent the occurrence of falls in young and old age groups. In addition, the role and impact of multidisciplinary treatment for hand injuries, such as physiotherapy, should be assessed.

6.4 Summary

Unlike hip and knee osteoarthritis, osteoarthritis in the joints of the hand has been less well studied. Hand IPJ osteoarthritis is also likely to be a different phenotype to large joint osteoarthritis, with different risk factors. This thesis has provided insight into the complex, multifactorial aetiology of IPJ osteoarthritis. It has also highlighted the importance of defining the disease, understanding the relationship between IPJ and first CMCJ osteoarthritis, and the gap of knowledge particularly surrounding symptomatic and clinical IPJ osteoarthritis. Gaining further understanding of hand,

and in particular IPJ osteoarthritis, should help physicians to better counsel, more appropriately investigate, and more successfully manage our patients in the clinic.

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8 APPENDIX

Appendix 2.1: REDCap questionnaire of risk factors for the incidence of IPJ osteoarthritis

Confidential

Risk factors for IPJ OA

Please refer to the scale below to rate how important you think each risk factor is for IPJ OA.

No importance

Minimal importance

Some importance

Strong importance

Extreme importance

[event-label]

I consent to my answers being collected, used, and stored for the purposes of this research	○ Yes ○ No
I consent to being acknowledged on relevant publications	○ Yes ○ No

a) Epidemiology and Demographics

	No importance	Minimal importance	Some importance	Strong importance	Extreme importance
1) Age	○	○	○	○	○
2) Occupation (For example- Retired, Professional, Manual etc)	○	○	○	○	○
3) Husband's occupation (For example- Retired, Professional, Manual etc)	○	○	○	○	○
4) Hand dominance	○	○	○	○	○
5) Smoking habits	○	○	○	○	○
6) Alcohol use	○	○	○	○	○

b) Activity level

	No importance	Minimal importance	Some importance	Strong importance	Extreme importance
1) Distance walked in a week	○	○	○	○	○
2) Extent of activity in job (For example- Sedentary, Active all day)	○	○	○	○	○
3) Time spent in sport over a week	○	○	○	○	○

	No importance	Minimal importance	Some importance	Strong importance	Extreme importance
4) GHQ (General Health Questionnaire) score	○	○	○	○	○

c) Obstetric and Gynaecology History

	No importance	Minimal importance	Some importance	Strong importance	Extreme importance
1) Age of menarche	○	○	○	○	○
2) Age of menopause	○	○	○	○	○
3) Number of live births	○	○	○	○	○
4) Number of miscarriages	○	○	○	○	○

d) History of Osteoarthritis (OA)

	No importance	Minimal importance	Some importance	Strong importance	Extreme importance
1) Back pain	○	○	○	○	○
2) Knee pain	○	○	○	○	○
3) Cervical spine OA	○	○	○	○	○
4) Lumbar spine OA	○	○	○	○	○
5) Shoulder OA	○	○	○	○	○
6) Elbow OA	○	○	○	○	○
7) Wrist OA	○	○	○	○	○
8) Hip OA	○	○	○	○	○
9) Knee OA	○	○	○	○	○
10) Ankle OA	○	○	○	○	○
11) MTPJ Foot OA	○	○	○	○	○

e) Drug History

	No importance	Minimal importance	Some importance	Strong importance	Extreme importance
1) Past use of oral contraceptive pill	○	○	○	○	○
2) Hormone replacement therapy	○	○	○	○	○
3) Antihypertensives	○	○	○	○	○
4) Diuretics	○	○	○	○	○
5) Diabetic medication	○	○	○	○	○
6) Calcium supplements	○	○	○	○	○
7) Steroids	○	○	○	○	○
8) Thyroid medication	○	○	○	○	○

f) Medical & Surgical History

	No importance	Minimal importance	Some importance	Strong importance	Extreme importance
1) Malignancy	○	○	○	○	○
2) Cardiovascular disease	○	○	○	○	○
3) Gastrectomy	○	○	○	○	○
4) Cholecystectomy	○	○	○	○	○
5) Hysterectomy	○	○	○	○	○
6) Oophorectomy	○	○	○	○	○
7) Other gynaecological surgery (Ie- Not Hysterectomy/ Oophorectomy)	○	○	○	○	○

g) Biomarkers

	No importance	Minimal importance	Some importance	Strong importance	Extreme importance
1) Type 2 collagen biomarkers C1 and C2	○	○	○	○	○
2) Type 2 collagen biomarker C2C	○	○	○	○	○
3) Type 2 collagen biomarker CPii	○	○	○	○	○
4) Cartilage biomarker CS846	○	○	○	○	○
5) Non-collagenous extracellular matrix protein hCOPM	○	○	○	○	○
6) Cartilage turnover biomarker CTX-ii	○	○	○	○	○
7) Serum C-Reactive Protein	○	○	○	○	○
8) Bone turnover biomarker CTX	○	○	○	○	○
9) Bone turnover biomarker PINP	○	○	○	○	○

h) Urine tests

	No importance	Minimal importance	Some importance	Strong importance	Extreme importance
1) Urine creatine	○	○	○	○	○
2) Urine bone turnover biomarker CTX	○	○	○	○	○

i) Haematology test

	No importance	Minimal importance	Some importance	Strong importance	Extreme importance
1) Oestradiol	○	○	○	○	○
2) DHEAS (Dehydroepiandrosterone Sulphate)	○	○	○	○	○
3) Fasting glucose	○	○	○	○	○
4) Total cholesterol	○	○	○	○	○
5) Triglyceride	○	○	○	○	○
6) HDL cholesterol	○	○	○	○	○

j) Family History

	No importance	Minimal importance	Some importance	Strong importance	Extreme importance
1) Mother Knee OA	○	○	○	○	○
2) Mother Hand OA	○	○	○	○	○
3) Maternal grandmother Knee OA	○	○	○	○	○
4) Maternal grandmother Hand OA	○	○	○	○	○
5) Any aunt Knee OA	○	○	○	○	○
6) Any aunt Hand OA	○	○	○	○	○
7) Father Knee OA	○	○	○	○	○
8) Father Hand OA	○	○	○	○	○
9) Any sister Knee OA	○	○	○	○	○
10) Any sister Hand OA	○	○	○	○	○
11) Any brother Knee OA	○	○	○	○	○
12) Any brother Hand OA	○	○	○	○	○
13) Any child/children Knee OA	○	○	○	○	○
14) Any child/children Hand OA	○	○	○	○	○
15) Mother Obesity	○	○	○	○	○
16) Father Obesity	○	○	○	○	○
17) Mother Hip fracture	○	○	○	○	○
18) Mother Wrist fracture	○	○	○	○	○
19) Mother Spine fracture	○	○	○	○	○
20) Maternal grandmother Hip fracture	○	○	○	○	○
21) Maternal grandmother Wrist fracture	○	○	○	○	○
22) Maternal grandmother Spine fracture	○	○	○	○	○
23) Any sister Hip fracture	○	○	○	○	○
24) Any sister Wrist fracture	○	○	○	○	○
25) Any sister Spine fracture	○	○	○	○	○
26) Any maternal aunt Hip fracture	○	○	○	○	○
27) Any maternal aunt Wrist fracture	○	○	○	○	○
28) Any maternal aunt Spine fracture	○	○	○	○	○

Other Risk Factors

	No	Yes
Are there any other risk factors you would like to suggest?	○	○

If yes, please specify

____

Appendix 3.1: Steps in the study design of a prediction/ prognostic model.

1. Study Design

Prediction model development studies are best addressed using a prospective cohort study (142). Cohort studies allow for a longitudinal time interval between the predictor measurement and the outcome, and, if treatment has not yet been received, allow the analysis of the natural course of the disease (142). Prospective cohort studies should also capture a sufficient number of individuals with the outcome, which can be used to inform power calculations, and allow the inclusions of multiple potential predictors in prediction model studies. However, developing a prospective cohort study if often difficult due to financial or time constraints, and instead, secondary analysis of data from cohorts established for other reasons are performed (142, 371).

Where data from cohort studies is not available, prediction models can be developed using data from case-control studies can also be used. However, as the ratio of cases to controls can be pre-determined, it is difficult to report the absolute risks (142, 372). This can be overcome by using a nested case-control study (in a cohort study with a known size) (373). Alternatively, data from randomised controls trials can also be used, with the treatment option included as a prognostic factor in the model (142). However, as the recruitment to trials is often based on strict criteria, the results a prognostic model developed using these factors are often not generalisable or transferable.

2. Outcome and Sample size

Outcomes should use 'hard' end-points, such as the incidence of disease, response to treatment, or progression of the disease (142). If 'soft' endpoints such as physiological measurements are used, they might not be true markers of outcomes that matter to patients. There should also be an adequate time period between the occurrence or measurement of the predictors, and the occurrence or measurement of the outcome, to allow sufficient time for outcome to become apparent (142). Finally, the outcome should be measured blinded to the predictors, to prevent bias (142).

The proportion of participants with the outcome should be used to inform sample size calculations. Sample size calculations are required to determine the degrees of freedom of all candidate predictors (prognostic factors or risk factors whilst they are being analysed in the model) which can be put into the model. If the sample size is small, or there is an imbalance caused by a high number of candidate predictors, the model might overfit the data (erroneously fit the data to noise, resulting in incorrectly decreased residual variation), and the model's performance might be overestimated. Traditionally, the rule of 10 events per variable has been used, which stipulates there must be 10 participants with the outcome per each candidate predictor (212, 374, 375). It has been suggested that this should be modified to 10 events per parameter, to take into account degrees of freedom, particularly for candidate predictors which have multiple levels (227). More recently, this has been superseded by more sophisticated sample size calculations, such as those based on the proportion of participants with the outcome and the r^2 (the proportion of variance in the outcome which can be explained by the candidate predictors) (227-229). There are also novel methods to adjust for overfitting, such as penalisation (375-381), though, if the tuning parameters have large uncertainty, the model could become mis-calibrated (281).

3. <u>Candidate predictors</u>

The importance of choosing candidate predictors is based on the fact that prognostic or prediction models do not test association. Therefore, using candidate predictors which have no clinical relevance or no biological plausibility might result in spurious results. Candidate predictors should also be standardised and reproducible, and easily applied to clinical practice, to ensure the model is generalisable (382). Candidate predictors should also be assessed for collinearity, to reduce the bias exerted by multiple collinear candidate predictors in the model. Selecting candidate predictors based on a univariate association with the outcome is not advised, as it does not improve the performance of the model (231).

When continuous candidate predictors are used, they should not be assumed to have a linear association with the outcome (231, 383). Instead, non-linear transformation should be tested, such as through the use of fractional polynomials or restricted cubic splines (231, 384, 385). Continuous candidate predictors should also not be categorised or dichotomised, as this results in loss of data granularity, an increase in residual confounding, and decreases the power of the model (259, 383). The cut-off points for categorising continuous data can also be arbitrary and does not reflect clinical practice, where many clinical measurements are often continuous, for example blood pressure (383).

When candidate predictors are put into the model, they can either be done so in a stepwise manner, or by putting all predictors into the model simultaneously. Stepwise methods include backwards elimination and forward selection. In backwards elimination, all candidate predictors are put into the model, and then deleted sequentially starting with the candidate predictor with a test statistic that is the lowest compared to a pre-determined threshold (386). However, backwards elimination is influenced by collinearity between candidate predictors, and once a candidate predictor is removed from the model, and cannot be re-added (296). In forwards selection, a candidate predictor is added to the model one at a time, and the test statistic is calculated (386, 387). If this test statistic is greater than a pre-determined threshold, the candidate predictor is included in the model. This continues for each candidate predictor until there are no remaining candidate predictors which are above the threshold. However, adding a candidate predictor to the model may result in a candidate predictor already in the model no longer meeting the threshold for inclusion (296). As candidate predictors cannot be removed from the model once inside it, it can be difficult to determine which candidate predictors are important for the outcome.

A combination of both backwards elimination and forward selection can be used, in which the assessment of candidate predictors starts with one of these methods, and at each iteration also uses the other method (296). For example, if forward selection is used first, once a candidate predictor is added to the model, the model is re-checked to remove any other candidate predictor using a backwards elimination approach. This method requires a large sample size, can be affected by collinearity between candidate predictors, and might use arbitrary thresholds (296, 388).

In a full model design, all of the candidate predictors are selected a priori and put into the model simultaneously. No candidate predictors are removed from the model. However, if there is a large number of candidate predictors, this method can result in a decreased power of the model and overfitting (231, 233).

4. Missing data

Both outcome and candidate predictor data should be assessed for any missingness, including both the amount of missing data and any patterns to the missing data. If ≤5% of data is missing and there are no patterns to the missingness, a complete case analysis can be used (i.e.- analysis of participants with no missing data) (272, 273). If >5% of data is missing, imputation methods can be used. A basic imputation method is single imputation, based on imputing the median or mean value of a variable for all missing data points (389). However, this can reduce the variance of the data, resulting in decreased model performance (231). It is also not reflective of clinical practice. A more robust and novel technique is to use multiple imputation, through which imputed values are taken from possible data points based on the distribution of the data. If there is ≤20% of missing data, it is recommended that this method is repeated 20 times for each data point, creating 20 multiple data sets (231). If there is >20% of missing data, the number of iterations should be equivalent to the percentage of missing data (390). A model can either be assessed separately on each of these imputed datasets and then the results pooled (275, 391), or all of the imputed datasets can be 'stacked' first, before the model is run on one larger dataset (392). If the model is initially run on each imputed dataset separately, in each of these datasets the continuous variables should be assessed for non-linearity with the outcome.

5. Statistical analysis

The type of statistical analysis used depends on the type of data in the model. If the outcome is only collected a one timepoint (for example, at the end of the study), a logistic regression can be used. The type of logistic regression might depend on the type of outcome data. For example, if the outcome is ordinal a proportional odds method can be used. Alternatively, if the outcome is measured at multiple time points and there is time to event data available, a Cox analysis (i.e.- survival analysis) can be performed. A survival analysis might be appropriate if the participants can be easily categorised into different subsets, or the disease has multiple phenotypes.

To prevent overfitting, the penalisation or shrinkage methods can then be used. However, penalisation methods have not yet been developed to be used in all types of models: for example, robust penalisation methods currently do not exist for proportional odds logistic regression models. In this case, the model should be internally validated instead. Internal validation involves testing the model on the dataset it was developed in. This can be done by splitting the data into a training set, in which the data is built, and a testing set, in which the data is internally validated. However, this decreases the power of the model during both development and validation. Instead, the model should be built using all of the data, and then internally validated using techniques such as bootstrapping and cross-validation. Bootstrapping takes a random sample of the data with replacement from the original dataset (231). It is advised to perform this over 500 iterations, though it is often feasible to use 2,000 iterations. Cross-validation splits the data into *k* folds, developing the data in *k-1* folds and testing it in the *kth* fold (231). This is repeated until each fold is used as the testing fold.

6. Model performance

The performance of the model should be assessed using discrimination and calibration assessments. Discrimination is the model's ability to differentiate between participants with and without the outcome, and can be measured using the concordance (C)-statistic (254, 255).

Calibration is the agreement between the predicted probabilities from the model and the observed outcomes in the dataset (258, 259). It can be visualised through a calibration slope plotted on a calibration plot. The calibration of a model can be expected to be 1 (i.e.- perfect calibration), as the model is both developed and tested on one dataset.

If internal validation techniques such as bootstrapping or cross-validation are used, the performance of the model can be assessed in each iteration. The optimism (the mean difference over the iterations) is subtracted from the performance of the model during the development, to give an optimism corrected performance (233).

7. External validation

The performance of the model in another dataset, ideally from a prospective cohort study, should also be tested, through external validation of the model (261, 393). There are two angles through which a model can be externally validated. The first is testing the generalisability of the model. This is similar to internal validation, as the model is tested in a new sample from the same population. An example of this type of testing would be performing temporal validation, through which different patients from the same population are recruited at a different time, and are used to test the model (263, 394). The second is to test the transportability of the model (395). This method tests the model in different but similar populations. For external validation to work well, the predictors should be similar in the development dataset and the external validation dataset. If the performance of the model is poor in the external validation datasets, the model can be re-calibrated by updating the intercept (396).

8. Clinical utility

Prediction or prognostic models can be used in clinical practice in the form of risk calculators, such as nomograms. However, models are only important if they improve clinical outcomes (397). This can be assessed through the use and the impact of models (398). The clinical use of models can be assessed through decision curve analyses for net benefit, the increase in the number of true positive diagnoses or outcomes from using the model, compared to a traditionally used clinical threshold (257, 265). The impact of using models should be studied in randomised controlled trials, assessing outcomes from using the model to not using the model.

Appendix 3.2: Candidate predictors in the model

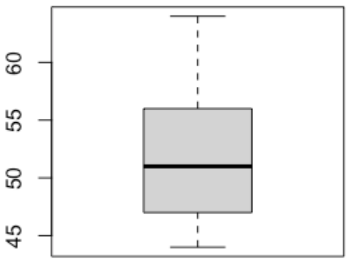
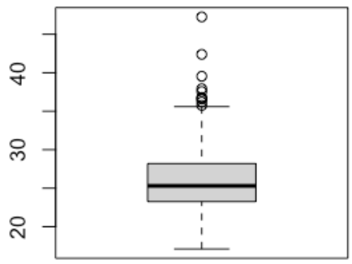
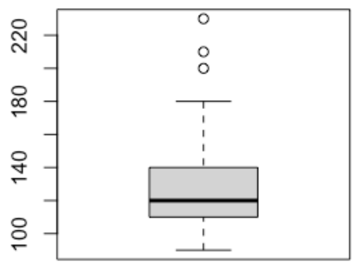
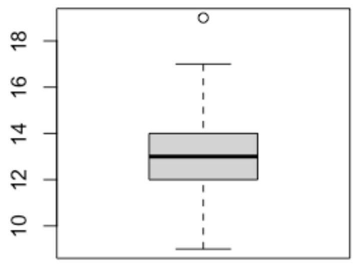
Candidate Predictor	Method of data collection
Age	Questionnaire at baseline: “Age of participant”. Response options using textbox (years)
Occupation	Questionnaire at baseline: “Occupation of participation”. Response options: “Housewife/ retired/ higher manager or professional/ skilled manager/ teacher/ nurse/ admin/ secretary/ clerical/ skilled manual/ unskilled manual/ cleaning/ domestic”. For the model, this was coded as manual (‘skilled manual’/ ‘unskilled manual’/ ‘cleaning or domestic’) or non-manual (housewife’/ ‘retired’/ ‘higher manager or professional’/ ‘skilled manager or teacher or nurse’/ ‘administrator or secretary or clerical’)
BMI	Examination at baseline: Weight (cm), Height (kg). BMI was calculated as weight (kg)/height $(m)^2$
Systolic blood pressure	Examination at baseline: Systolic blood pressure (mmHg)
History of hand fracture	Questionnaire at nine years’ follow-up: “Have you had a fracture”. Response options “yes/no”. If “yes”, using branched logic, “What bone did you fracture”. Response options “hand (MCP/finger)/ upper limb/ wrist/ foot/ lower limb/ rib/ hip/ vertebra/ coccyx/ nose/ femoral shaft/ skull/ unknown”. If “yes”, using branched logic, “On what date did the fracture happen?” Response options using textbox (date) For the model, a composite variable was produced. If the response option for the first question was “yes”, and fracture of the “hand (MCP/finger)” was listed, and this fracture occurred before the baseline year, this was converted to a composite variable for “history of hand fracture” with binary “yes/no” response options. This was to capture whether to not had a participant had a history of hand fracture at baseline.
Age at menarche	Questionnaire at baseline: “Age at menarche”. Response options using textbox (years)
Reached menopause	Questionnaire at baseline: “Age of menopause”. Response options using textbox (years). Participants who had not reached menopause were coded with variable “99” For the model, this was converted to a binary “yes/no” response options, to capture whether or not a participant had reached menopause.
Live births	Questionnaire at baseline: “Number of live births”. Response options using textbox (number). Participants who did not have any live births were coded with variable “99”.

	For the model, this was converted to a binary "yes/no" response options, to capture whether or not a participant had experienced any live births.
Miscarriages	Questionnaire at baseline: "Number of miscarriages". Response options using textbox (number). Participants who did not have any miscarriages were coded with variable "99". For the model, this was converted to a binary "yes/no" response options, to capture whether or not a participant had experienced any miscarriages.
Hysterectomy	Questionnaire at baseline: "Ever had a hysterectomy". Response options using binary "yes/no".
Use of oral contraceptive pill	Questionnaire at baseline: "Use of oral contraceptive pill". Response options using binary "yes/no".
Use of hormone replacement therapy	Questionnaire at baseline: "Ever undergone hormone replacement therapy". Response options using binary "yes/no".
Smoking	Questionnaire at baseline: "Smoke". Response options "never/ current/ ex". For the model, a composite variable was produced, using binary "ever/never" response options. If the response option in the questionnaire was either "current" or "ex", the outcome was coded as "ever" for the model. If the response option in the questionnaire was "never" the outcome was coded as "never" for the model.
Alcohol use	Questionnaire at baseline: "Alcohol frequency". Response options "never/ weekly/ social occasions". For the model, a composite variable was produced, using binary "ever/never" response options. If the response option in the questionnaire was either "weekly" or "social occasions", the outcome was coded as "ever" for the model. If the response option in the questionnaire was "never" the outcome was coded as "never" for the model.
History of knee osteoarthritis in family	Questionnaire at baseline: "Family history of knee arthritis with mother". Response options "none/ probable/ definite/ adopted". "Family history of knee arthritis with maternal grandmother". Response options "none/ probable/ definite/ adopted". "Family history of knee arthritis with aunt". Response options "none/ probable/ definite/ adopted". "Family history of knee arthritis with father". Response options "none/ probable/ definite/ adopted". "Family history of knee arthritis with sister". Response options "none/ probable/ definite/ adopted". "Family history of knee arthritis with brother". Response options "none/ probable/ definite/ adopted". "Family history of knee arthritis with children". Response options "none/ probable/ definite/ adopted".

	For the model, a composite variable was produced, for “family history of knee osteoarthritis”, using binary “yes/no” response options. If any response option in the questionnaire was either “probable” or “definite”, the outcome was coded as “yes” for the model. If any response option in the questionnaire was either “probable” or “definite”, the outcome was coded as “no” for the model. If all response options in the questionnaire were “adopted”, the outcome was coded as “missing” for the model.
History of hand osteoarthritis in family	Questionnaire at baseline: “Family history of hand arthritis with mother”. Response options “none/ probable/ definite/ adopted”. “Family history of hand arthritis with maternal grandmother”. Response options “none/ probable/ definite/ adopted”. “Family history of hand arthritis with aunt”. Response options “none/ probable/ definite/ adopted”. “Family history of hand arthritis with father”. Response options “none/ probable/ definite/ adopted”. “Family history of hand arthritis with sister”. Response options “none/ probable/ definite/ adopted”. “Family history of hand arthritis with brother”. Response options “none/ probable/ definite/ adopted”. “Family history of hand arthritis with children”. Response options “none/ probable/ definite/ adopted”. For the model, a composite variable was produced, for “family history of hand osteoarthritis”, using binary “yes/no” response options. If any response option in the questionnaire was either “probable” or “definite”, the outcome was coded as “yes” for the model. If any response option in the questionnaire was either “probable” or “definite”, the outcome was coded as “no” for the model. If all response options in the questionnaire were “adopted”, the outcome was coded as “missing” for the model.
Osteoarthritis in knee	Bilateral knee radiographs at baseline, read using the Kellgren-Lawrence atlas for each knee (Response options “0” for none, “1” for possible osteophyte, “2” for definite osteophyte and possible joint space narrowing, “3” for definite osteophyte and definite joint space narrowing, “4” for definite osteophyte and bone on bone joint space narrowing”, “5” for total knee replacement). For the model, a composite variable was produced, using binary “yes/no” response options. If at least one knee was scored ≥2, the outcome was coded as “yes”. If both knees were scored <2, the outcome was scored as “no”.
Osteoarthritis in first carpometacarpal joint	Bilateral hand radiographs at baseline, read using the Kellgren-Lawrence atlas for each hand (Response options “0” for none, “1” for possible osteophyte, “2” for definite osteophyte and possible joint space narrowing, “3” for definite osteophyte and definite joint space narrowing, “4” for definite osteophyte and bone on bone joint space narrowing”). For the model, a composite variable was produced, using binary “yes/no” response options. If at least one first carpometacarpal joint was scored ≥2, the outcome was coded as “yes”. If both carpometacarpal joints were scored <2, the outcome was scored as “no”.

BMI: Body mass index

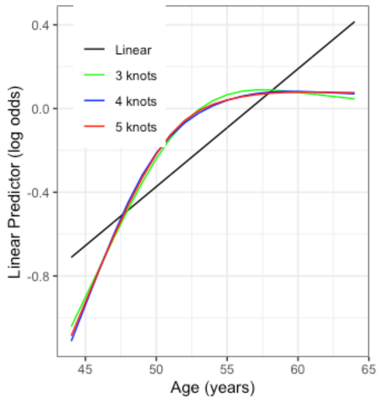
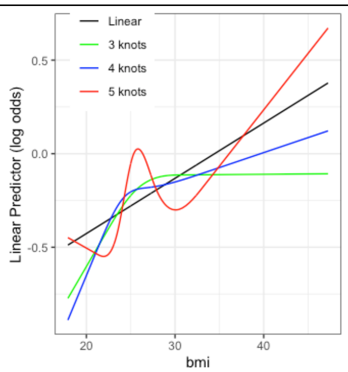
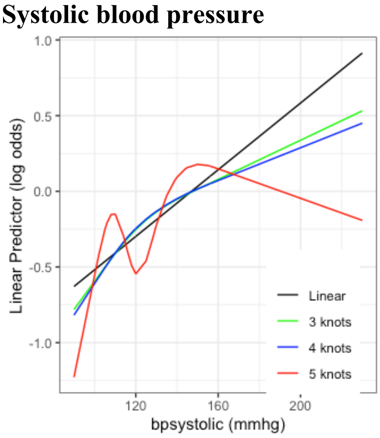
Appendix 3.3: Assessing outliers for age, BMI, systolic blood pressure, and age at menarche, for incident IPJ osteoarthritis in The Chingford 1000 Women Study

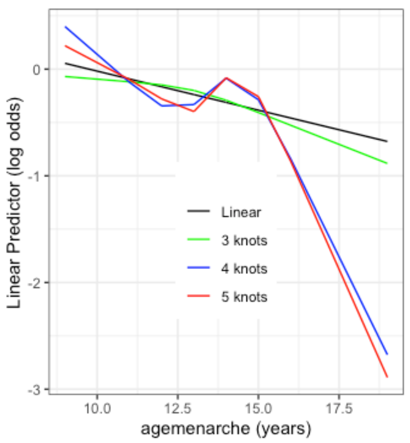
Candidate predictor	Value of Outliers	Boxplot
Age	No outliers	
BMI	39.54214 36.78652 36.66270 42.38548 36.57133 35.75596 47.25510 37.55205 37.92385 36.19875 *Outliers are all plausible*	
Systolic blood pressure	200 230 210 *Outliers are not clinically acceptable. Therefore, these values will be coded as NA (exclude in the complete case model, but imputed in the imputation model)*	
Age at menarche	19 *Outlier is plausible*	

Appendix 3.4: Testing linearity for age, BMI, systolic blood pressure, and age at menarche, for incident IPJ osteoarthritis in The Chingford 1000 Women Study

Knots are placed in pre-specified locations. (233)
3 knots are placed at the 10th, 50th, and 90th percentiles
4 knots are placed at the 5th, 35th, 65th, and 95th percentiles
5 knots are placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles

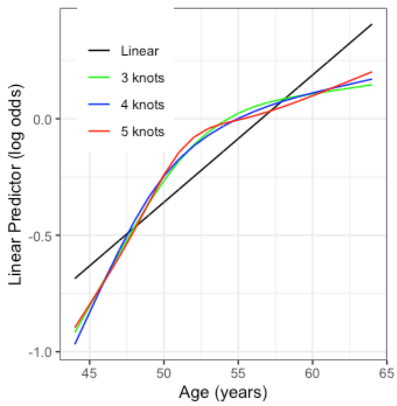
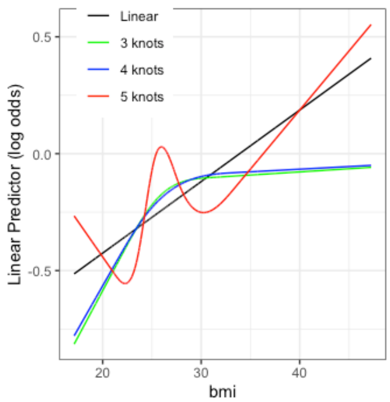
3.4a For complete case analysis

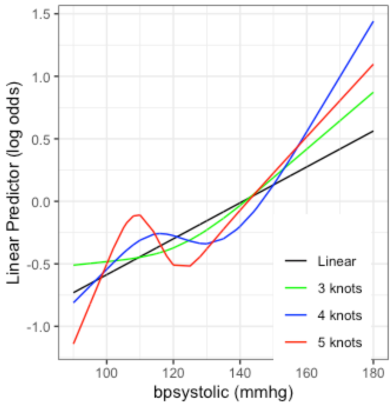
Graph	AIC	Significance of coefficients
 **Age** *All are biologically plausible*	Linear: 578.20 3knotsmodel: 577.41 4knotsmodel: 579.39 5knotsmodel: 581.36 *AIC is lowest for 3 knots model*	**Linear:** Statistically significant **3 knots:** 2 and 3 knots are statistically significant **4 knots:** No statistical significance **5 knots:** No statistical significance
 **BMI** *Linear and 3 knots are biologically plausible*	Linear: 586.61 3knotsmodel: 588.36 4knotsmodel: 589.93 5knotsmodel: 588.74 *AIC is lowest for linear model*	**Linear:** No statistical significance **3 knots:** No statistical significance **4 knots:** No statistical significance **5 knots:** 5 knots only is statistically significance
Systolic blood pressure  *Linear, 3 & 4 knots models are biologically plausible*	Linear: 579.43 3knotsmodel: 580.98 4knotsmodel: 580.74 5knotsmodel: 580.89 *AIC is lowest for linear*	**Linear:** Statistically significant **3 knots:** Not statistically significant **4 knots:** Not statistically significant **5 knots:** 3 & 4 knots are statistically significant

Age at menarche 	Linear: 587.14 3knotsmodel: 588.92 4knotsmodel: 587.22 5knotsmodel: 588.98 *AIC is lowest for linear model*	**Linear:** Not statistically significant **3 knots:** Not statistically significant **4 knots:** 4 knots is statistically significant **5 knots:** Not statistically significant

AIC: Akaike information criterion

3.4b For imputed analysis using MICE

Graph	AIC	Statistical significant of coefficients
 **Age** *All are biologically plausible*	Linear: 12404.53 3knotsmodel: 12377.56 4knotsmodel: 12379.6 5knotsmodel: 12380.6 *AIC is lowest for 3 knots model*	**Linear:** Statistically significant **3 knots:** 2 and 3 knots are statistically significant **4 knots:** 2, 3 and 4 knots are statistically significant **5 knots:** 2 knots is statistically significant
 **BMI** *Linear and 3 knots models are biologically plausible*	Linear: 12565.15 3knotsmodel: 12554.04 4knotsmodel: 12559.08 5knotsmodel: 12513.31 *AIC is lowest for 5 knots model*	**Linear:** Statistically significant **3 knots:** 2 and 3 knots are statistically significant **4 knots:** 2 knots is statistically significant **5 knots:** 2,3 and 4 knots are statistically significant

<table>
<tr>
<td>Systolic blood pressure


Linear and 3 knots models are biologically plausible</td>
<td>Linear: 12443.52

3knotsmodel:12429.13

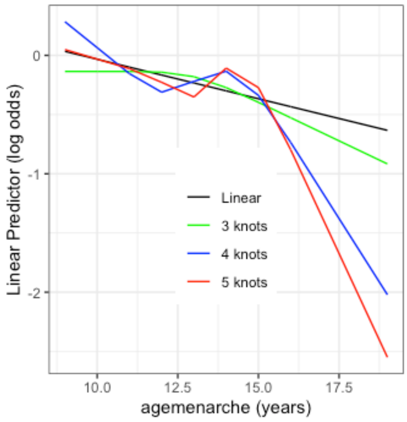
4knotsmodel: 12387.22

5knotsmodel: 12326.55

AIC is lowest for 5 knots model</td>
<td>Linear:
Statistically significant

3 knots:
3 knots statistically significant

4 knots:
2, 3 and 4 statistically significant

5 knots:
2, 3, 4 and 5 knots statistically significant</td>
</tr>
<tr>
<td>Age at menarche

</td>
<td>Linear: 12571.45

3knotsmodel: 12567.85

4knotsmodel: 12529.31

5knotsmodel: 12516.17

AIC is lowest for 5 knots model</td>
<td>Linear:
Statistically significant

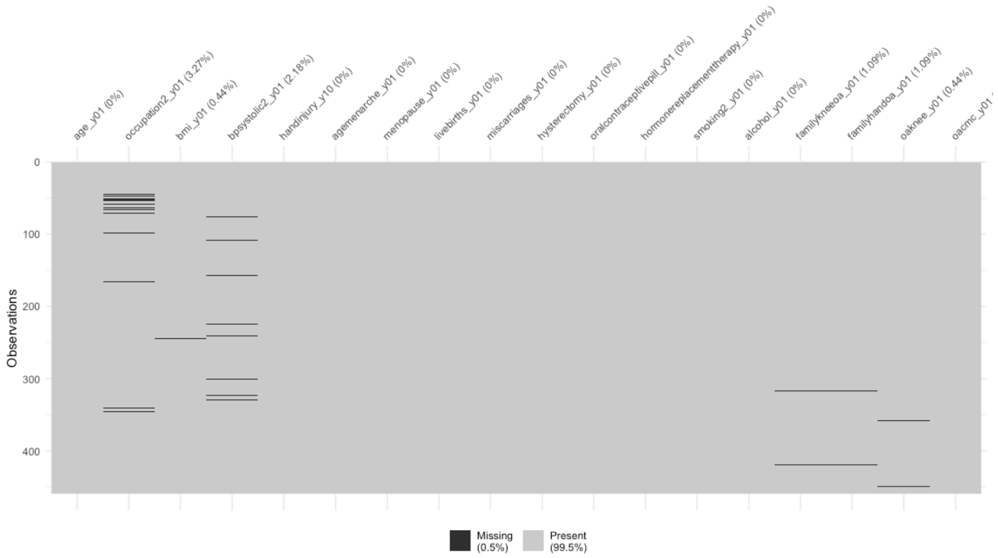
3 knots:
3 knots is statistically significant

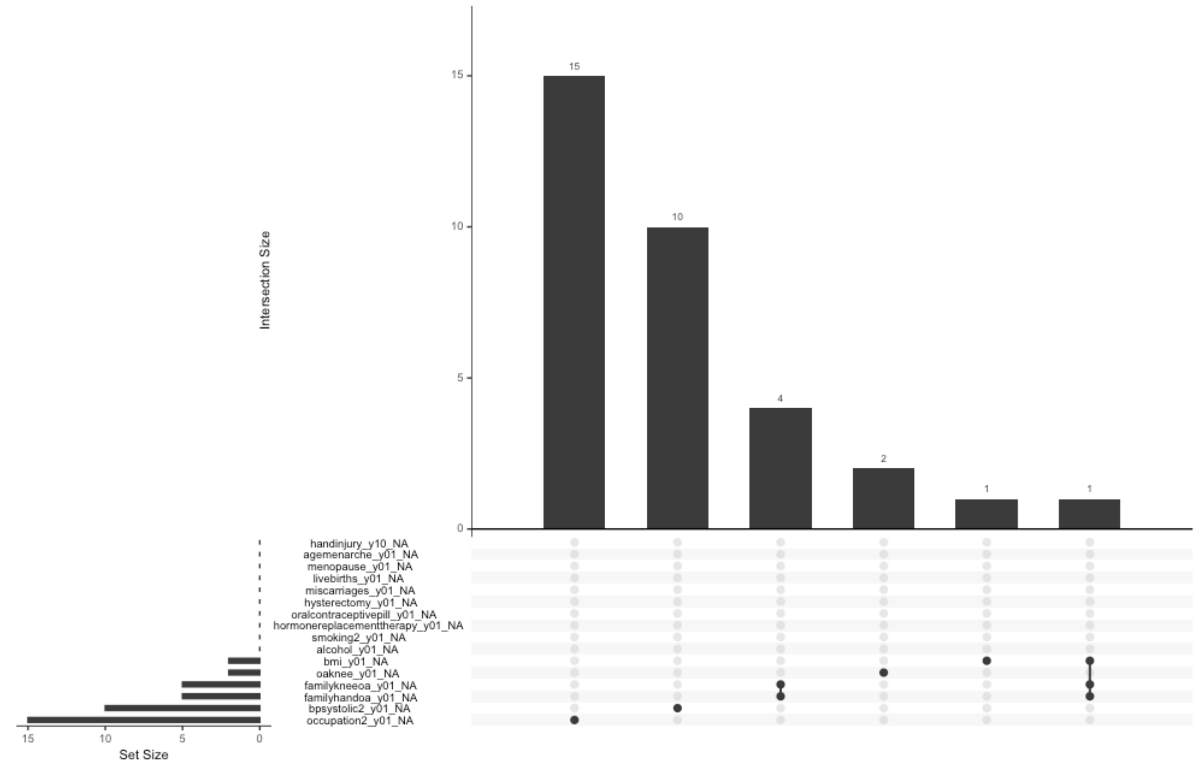
4 knots:
2, 3 and 4 knots are statistically significant

5 knots:
4 and 5 knots are statistically significant</td>
</tr>
</table>

Appendix 3.5: Missing data in The Chingford 1000 Women Study

Appendix 3.5a: Patterns of missingness across two pictorials



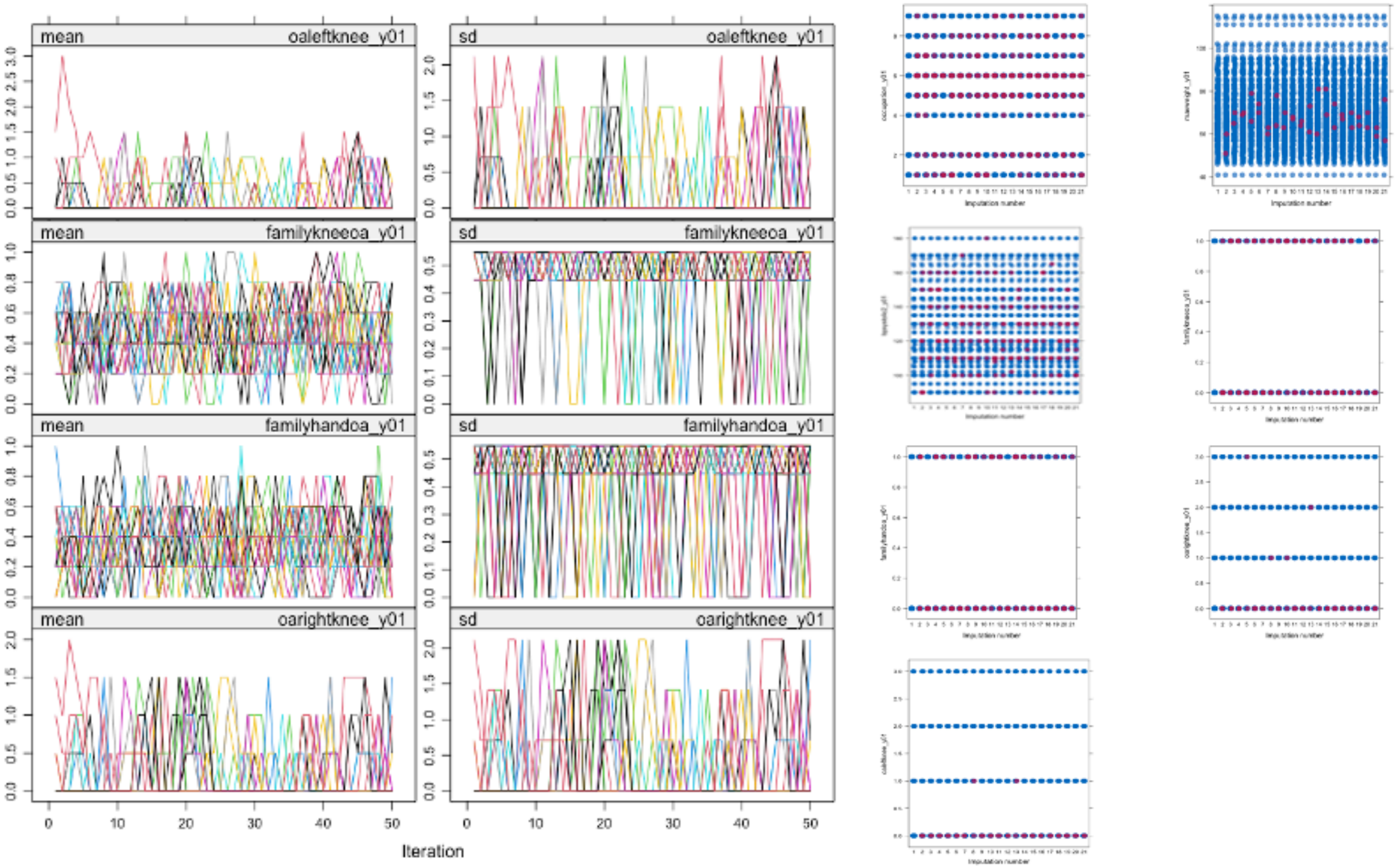


Appendix 3.5b: Comparison between participants with and without missing data

Predictor	Participants with complete data N=426	Participants with missing data N= 33
Age (years) [median (IQR)]	51 (9)	51 6)
Occupation [n (%)]		
Non-manual	349 (82)	16 (89)
Manual	77 (18)	2 (11)
		Missing: 15
BMI (kg/m²) [mean(SD)]	25.28 (4.84)	25.64 (5.59)
Systolic blood pressure (mmHg) [mean(SD)]	120 (28)	120 (27.5)
History of hand fracture [n (%)]		
No	421 (99)	32 (97)
Yes	5 (1)	1 (3)
Age at menarche (years) [median (IQR)]	13 (2)	13 (2)
Reached menopause [n (%)]		
No	139 (33)	12 (36)
Yes	287 (67)	21 (64)
Live births [n (%)]		
No	55 (13)	7 (21)
Yes	371 (87)	26 (79)
Miscarriage [n (%)]		
No	284 (67)	18 (55)
Yes	142 (33)	15 (45)
Hysterectomy [n (%)]		
No	330 (77)	28 (85)
Yes	96 (23)	5 (15)
Use of oral contraceptive pill [n (%)]		
No	256 (60)	17 (52)
Yes	170 (40)	16 (48)
Use of hormone replacement therapy [n (%)]		
No	325 (76)	17 (52)
Yes	101 (24)	16 (48)
Smoking [n (%)]		
Never	234 (55)	55 (67)
Ever	192 (45)	45 (33)
Alcohol use [n (%)]		
Never	59 (14)	3 (9)
Ever	367 (86)	30 (91)
History of knee osteoarthritis in family [n (%)]		
No	216 (51)	16 (57)
Yes	210 (49)	12 (42)
		Missing: 5
History of hand osteoarthritis in family [n (%)]		
No	259 (61)	22 (79)
Yes	167 (39)	6 (21)
		Missing: 5
Osteoarthritis in ≥1 knee joint (KL≥2) [n (%)]		
No	387 (91)	27 (87)
Yes	39 (9)	4 (13)
		Missing: 2
Osteoarthritis in ≥1 first CMCJ (KL≥2) [n (%)]		
No	367 (86)	27 (82)
Yes	59 (14)	6 (18)

BMI: Body mass index; CMCJ: Carpometacarpal joint; IQR: Interquartile range; KL: Kellgren Lawrence; SD: Standard deviation

Appendix 3.6: Assessment of imputed data



Left: Stems of the means and standard deviations were plotted and all showed intermingling, confirming there were no trends
Right: Observed and imputed data were plotted, and no trends were found (Blue: Observed data; Pink: Imputed data)

Appendix 3.7: Model built in participants with complete case data

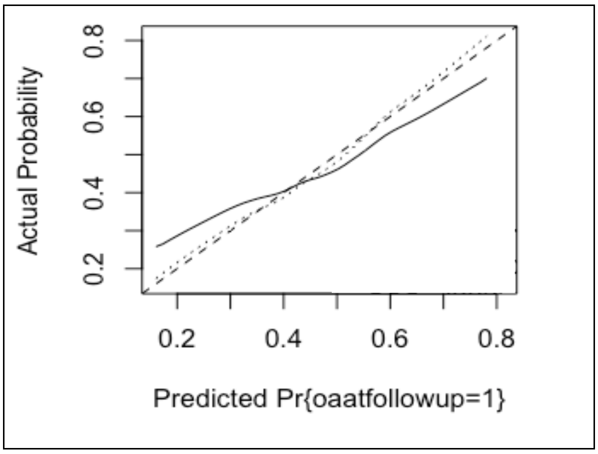
3.7a Coefficients, standard errors, p values and odds ratios for the prediction model for incident IPJ osteoarthritis

Predictor	B coefficient	Standard error	p value	Odds ratio	95% confidence interval
Intercept	-4.80	3.47	<0.005	0.0002	0.000000038 to 0.03
Age (years): RCS: Knot 2	0.07	0.07	<0.005	1.17	1.06 to 1.39
Knot 3	-0.06	0.10	0.05	0.84	0.66 to 0.96
Occupation	0.58	0.28	0.01	1.92	1.16 to 3.43
BMI (kg/m^2)	0.02	0.03	0.50	1.02	0.96 to 1.08
BP systolic	0.01	0.01	0.80	1.01	1.00 to 1.02
Hand fracture	n/a	n/a	n/a	1.00	0.12 to 10.1
Age at menarche	0.09	0.06	0.11	0.91	0.79 to 1.02
Menopause	0.02	0.33	0.61	0.92	0.44 to 1.61
Live births	0.04	0.32	0.74	0.92	0.47 to 1.67
Miscarriages	n/a	n/a	n/a	1.00	0.66 to 1.62
Hysterectomy	-0.11	0.28	0.66	0.89	0.50 to 1.54
Oral contraceptive pill	-0.12	0.34	0.69	0.91	0.57 to 1.44
Hormone replacement therapy	-0.36	0.26	0.09	0.66	0.38 to 1.07
Smoking	0.16	0.22	0.27	1.22	0.83 to 1.94
Alcohol use	0.31	0.31	0.27	1.38	0.77 to 2.62
Family knee OA	-0.18	0.23	0.41	0.83	0.53 to 1.30
Family hand OA	-0.04	0.24	0.69	0.93	0.57 to 1.45
OA Knee	-0.18	0.37	0.59	0.84	0.39 to 1.70
OA CMCJ	0.59	0.31	0.03	1.90	1.08 to 3.59

95% CI: 95% Confidence interval; BMI: Body mass index; BP: Blood pressure; CMCJ: Carpometacarpal joint; OA: Osteoarthritis; RCS: Restricted cubic spline (age was modelled using a three-knot term)

History of hand fracture and history of miscarriages were removed from the model (coefficient shrunk to 0)

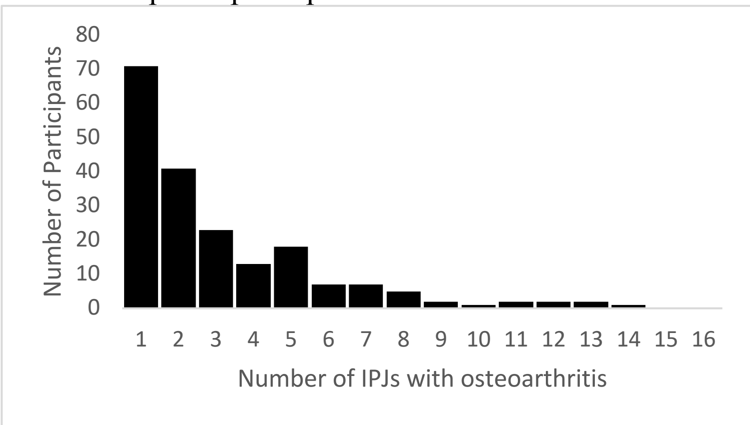
The discrimination of the model was good (C-statistic: 0.67, 95% CI: 0.62 to 0.72), but the model was mis-calibrated (calibration slope: 1.00, 95% CI: 0.68 to 1.34)



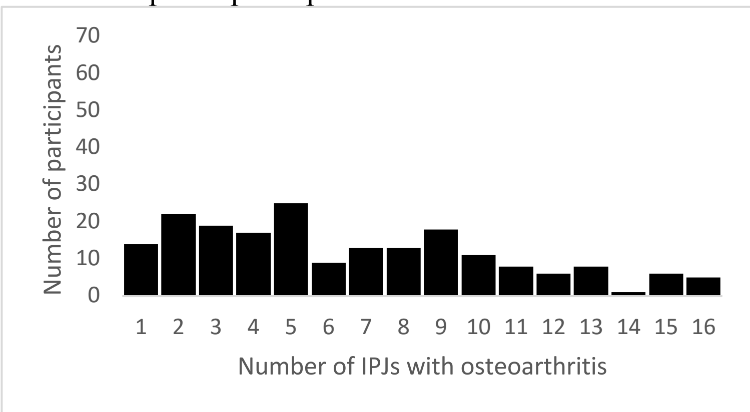
3.7b: Calibration plot of the prediction model for incident IPJ osteoarthritis, built using participants with complete case data

Appendix 4.1: Distribution of participants per number of IPJs with progression in The Chingford 1000 Women Study

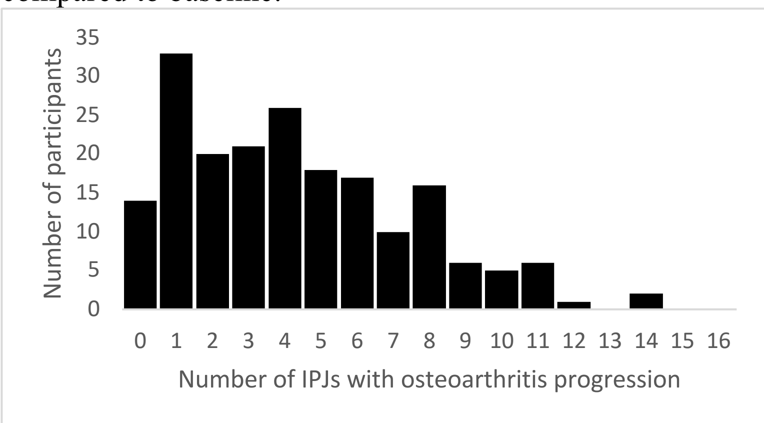
Number of participants per number of IPJs with osteoarthritis at baseline:



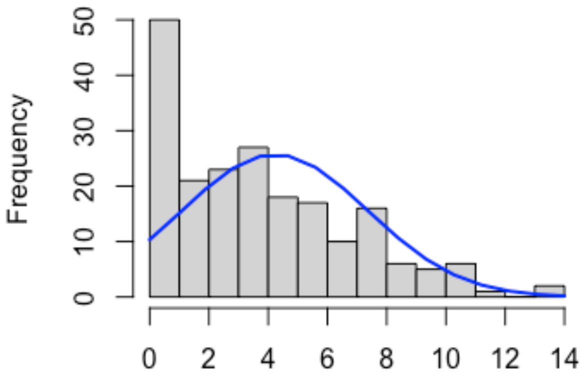
Number of participants per number of IPJs with osteoarthritis at follow up:



Number of participants per number of IPJs with osteoarthritis progression at follow up compared to baseline:

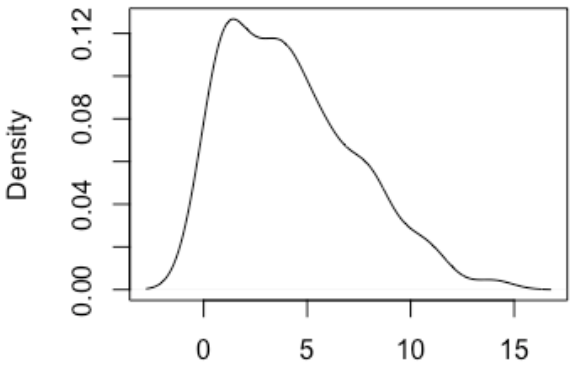


Histogram of number of participants per number of IPJs with osteoarthritis progression at follow up compared to baseline:



Number of IPJs with osteoarthritis progression

Kernel Density plot of number of participants per number of IPJs with osteoarthritis progression at follow up compared to baseline:



Number of IPJs with osteoarthritis progression

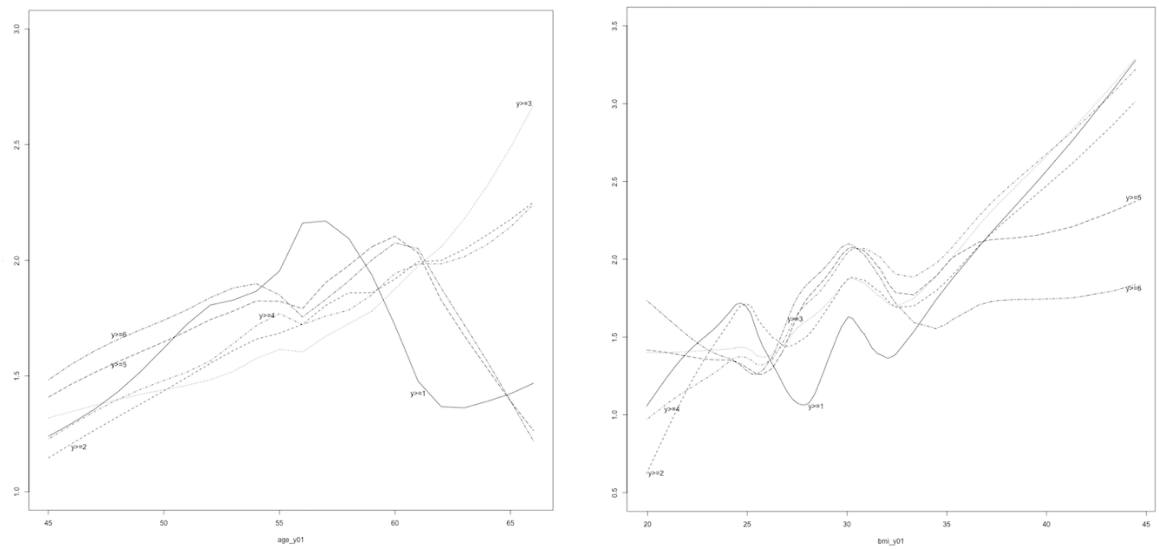
IPJs: Interphalangeal joints
Osteoarthritis was defined as ≥2 KL in ≥1 IPJ
Osteoarthritis progression was defined as an increase of ≥1 KL grade in ≥1 IPJ at follow up compared to baseline

Appendix 4.2: Candidate predictors in the model

Candidate predictor	Method of data collection in Chingford Study	Method of data collection in JoCo Project
Age	Questionnaire at baseline: “Age of participant”. Response options using textbox (years)	Questionnaire at baseline: “Age”. Response options using textbox (years)
BMI	Examination at baseline: Weight (cm), Height (kg). BMI was calculated as weight (kg)/height $(m)^2$	Questionnaire at baseline: “BMI”. Response options using textbox (kg/m^2)
Occupation	Questionnaire at baseline: “Occupation of participation”. Response options: “Housewife/ retired/ higher manager or professional/ skilled manager/ teacher/ nurse/ admin/ secretary/ clerical/ skilled manual/ unskilled manual/ cleaning/ domestic”. For the model, this was coded as manual (‘skilled manual’/ ‘unskilled manual’/ ‘cleaning or domestic’) or non-manual (housewife’/ ‘retired’/ ‘higher manager or professional’/ ‘skilled manager or teacher or nurse’/ ‘administrator or secretary or clerical’)	Questionnaire at baseline “Longest job?” Response options: “farming or forestry or fishing/ managerial and professional/ operator or fabricator or labourer/ precision production or craft or repair/ service/ military/ technical or sales and administrative support”. For the model, this was coded as manual (‘farming or forestry or fishing’/ ‘operator or fabricator or labourer’/ ‘precision production or craft or repair’/ ‘service’/ ‘military’), or non-manual (‘managerial or professional’/ ‘technical or sales or administrative support’)
Osteoarthritis in first carpometacarpal joint	Bilateral hand radiographs at baseline, read using the Kellgren-Lawrence atlas for each hand (Response options “0” for none, “1” for possible osteophyte, “2” for definite osteophyte and possible joint space narrowing, “3” for definite osteophyte and definite joint space narrowing, “4” for definite osteophyte and bone on bone joint space narrowing”.	Bilateral hand radiographs at baseline, read using the Kellgren-Lawrence atlas for each hand (Response options “0” for none, “1” for possible osteophyte, “2” for definite osteophyte and possible joint space narrowing, “3” for definite osteophyte and definite joint space narrowing, “4” for definite osteophyte and bone on bone joint space narrowing”.

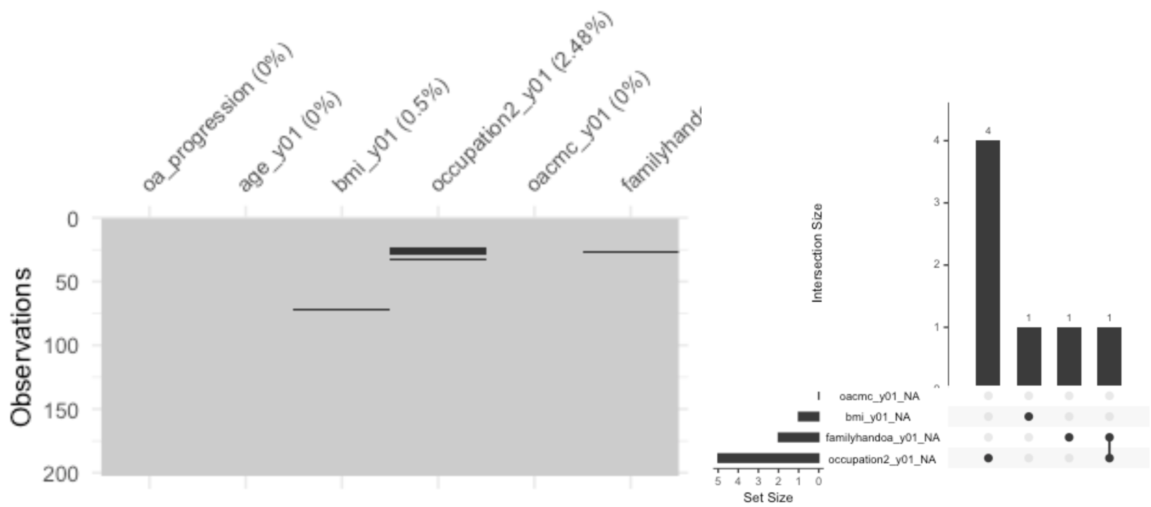
	For the model, a composite variable was produced, using binary “yes/no” response options. If at least one first carpometacarpal joint was scored ≥2, the outcome was coded as “yes”. If both carpometacarpal joints were scored <2, the outcome was scored as “no”.	For the model, a composite variable was produced, using binary “yes/no” response options. If at least one first carpometacarpal joint was scored ≥2, the outcome was coded as “yes”. If both carpometacarpal joints were scored <2, the outcome was scored as “no”.
History of osteoarthritis in family	Questionnaire at baseline: “Family history of hand arthritis with mother”. Response options “none/ probable/ definite/ adopted”. “Family history of hand arthritis with maternal grandmother”. Response options “none/ probable/ definite/ adopted”. “Family history of hand arthritis with aunt”. Response options “none/ probable/ definite/ adopted”. “Family history of hand arthritis with father”. Response options “none/ probable/ definite/ adopted”. “Family history of hand arthritis with sister”. Response options “none/ probable/ definite/ adopted”. “Family history of hand arthritis with brother”. Response options “none/ probable/ definite/ adopted”. “Family history of hand arthritis with children”. Response options “none/ probable/ definite/ adopted”. For the model, a composite variable was produced, for “family history of hand osteoarthritis”, using binary “yes/no” response options. If any response option in the questionnaire was either “probable” or “definite”, the outcome was coded as “yes” for the model. If any response option in the questionnaire was either “probable” or “definite”, the outcome was coded as “no” for the model. If all response options in the questionnaire were “adopted”, the outcome was coded as “missing” for the model.	Questionnaire at baseline: “Has a family history of arthritis or joint trouble”, using binary “yes/no” response options.

Appendix 4.3: Testing linearity for age (right side) and BMI (left side) with each level of the outcome in The Chingford 1000 Women Study

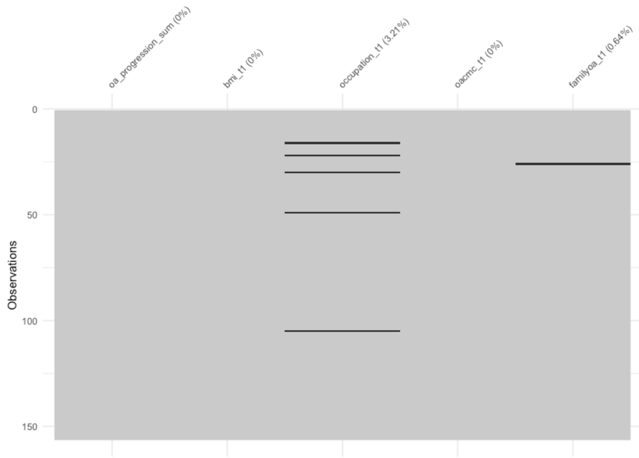


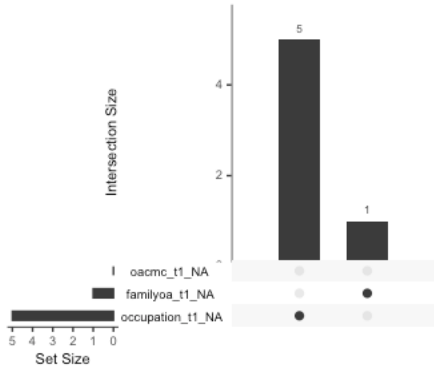
BMI: Body mass index

Appendix 4.4: Patterns of missingness in The Chingford 1000 Women Study



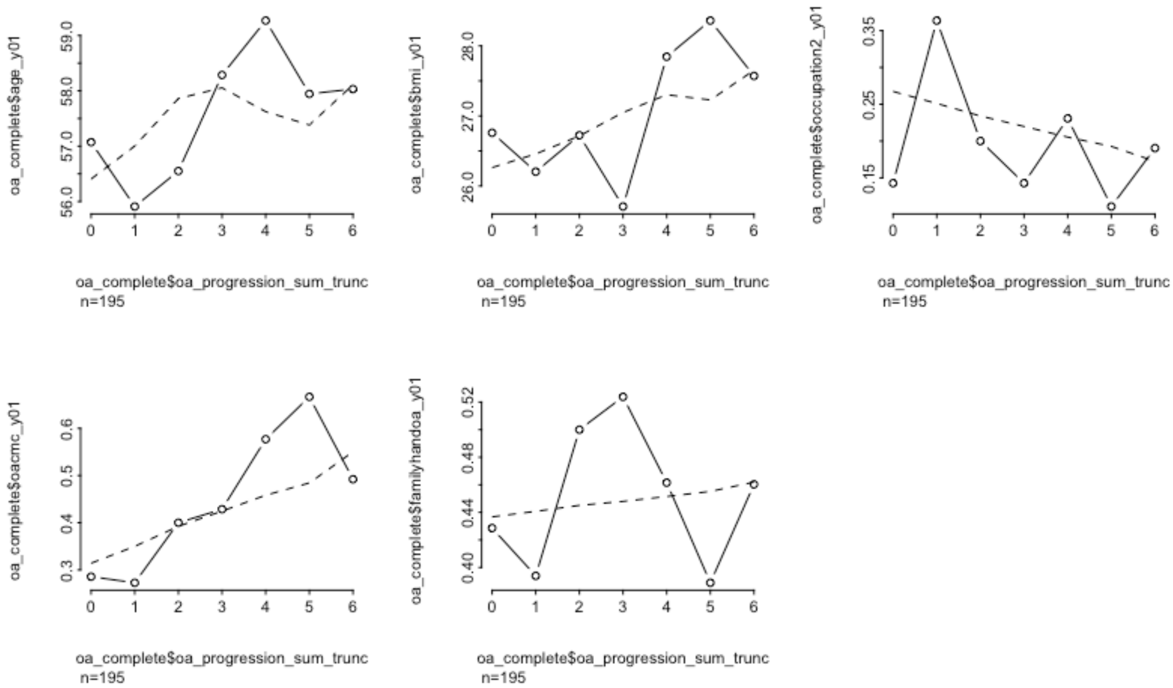
Appendix 4.5: Patterns of missingness in The Johnston County Osteoarthritis Project used for external validation



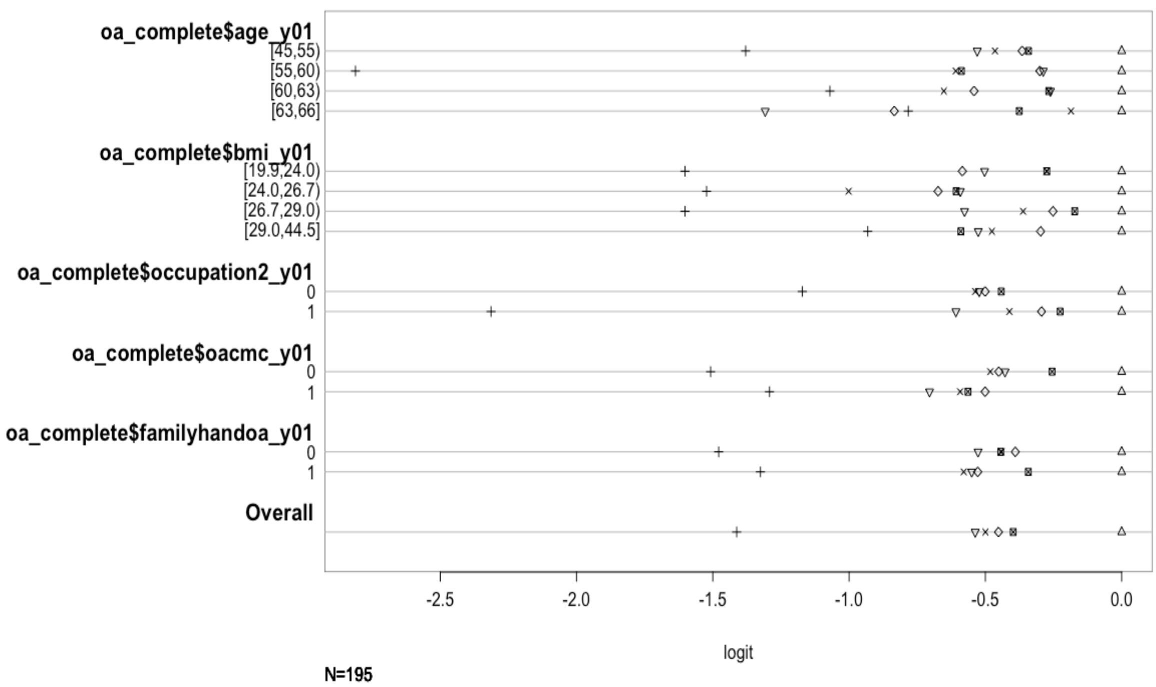


Appendix 4.6: Assumptions of proportional odds in the original model

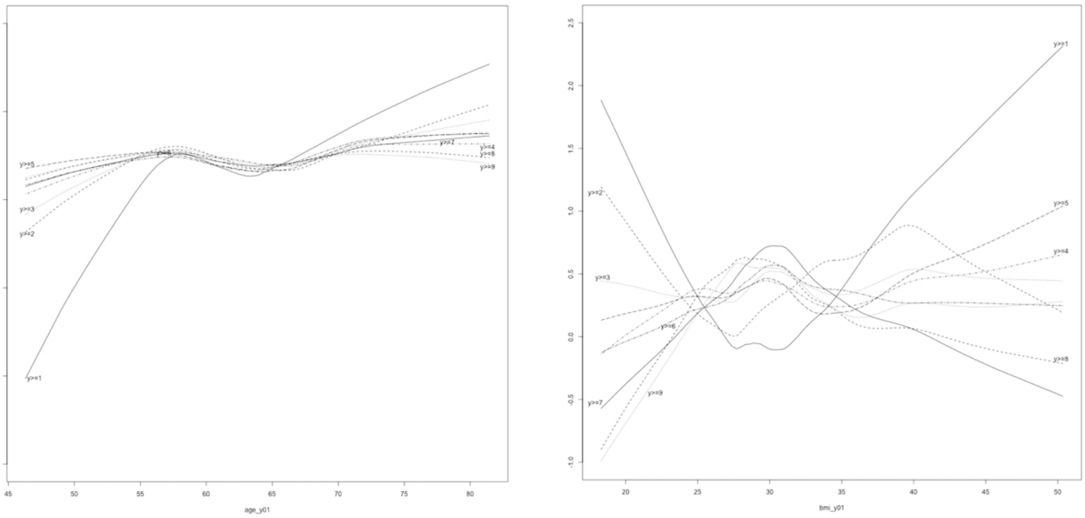
Stratifying the means of the predictors by the levels of the outcome:



Visualising the logits for all levels of the outcome for each level of the predictors:

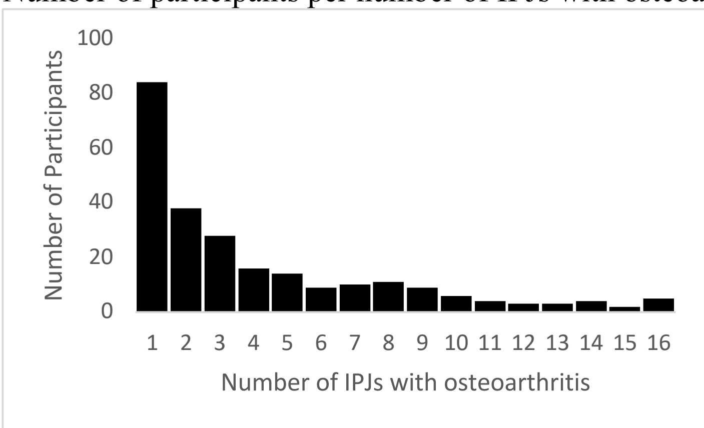


Appendix 4.7: Testing linearity for age (right side) and BMI (left side) with each level of the outcome in The Johnston County Osteoarthritis Project

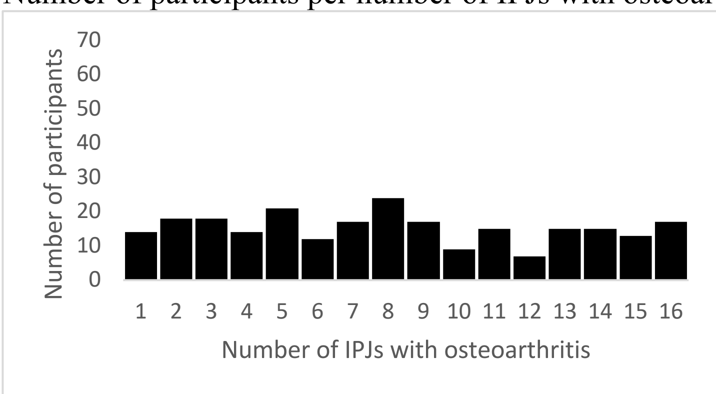


Appendix 4.8: Distribution of participants per number of IPJs with progression in The Johnston County Osteoarthritis Project

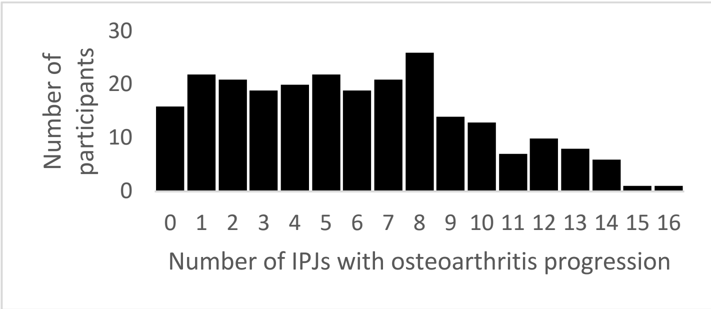
Number of participants per number of IPJs with osteoarthritis at baseline:



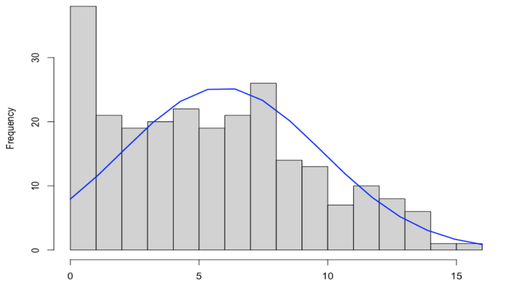
Number of participants per number of IPJs with osteoarthritis at follow up:



Number of participants per number of IPJs with osteoarthritis progression at follow up compared to baseline:

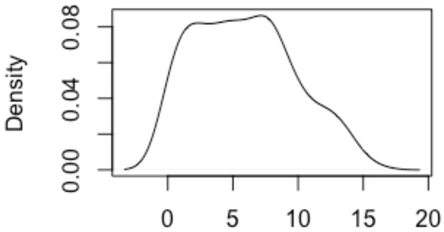


Histogram of number of participants per number of IPJs with osteoarthritis progression at follow up compared to baseline:



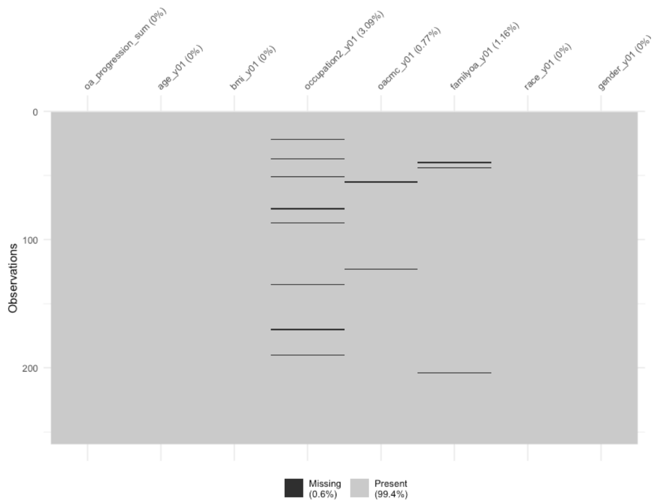
Number of IPJs with osteoarthritis progression

Kernel Density plot of number of participants per number of IPJs with osteoarthritis progression at follow up compared to baseline:



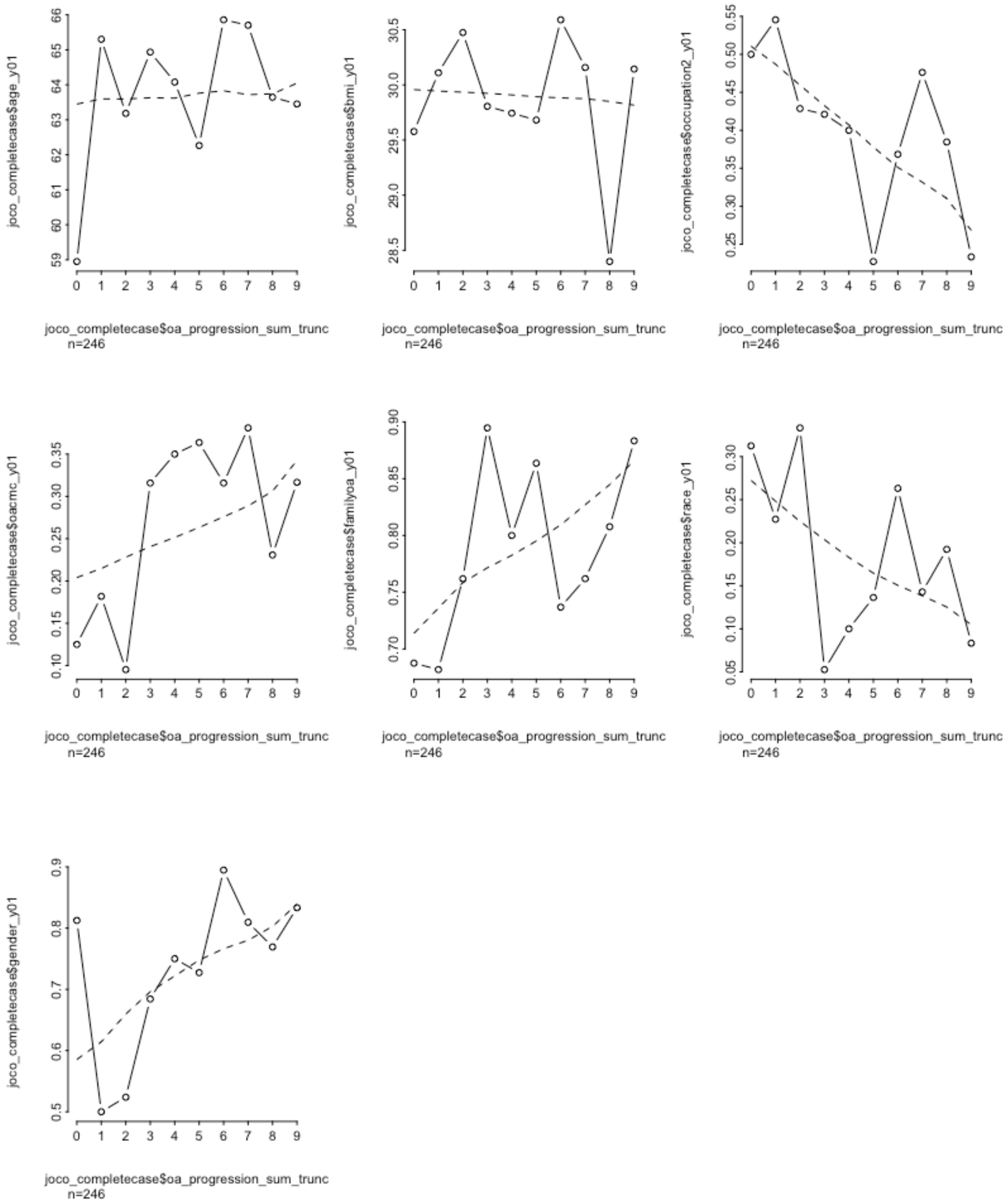
Number of IPJs with osteoarthritis progression

Appendix 4.9: Patterns of missingness in The Johnston County Osteoarthritis Project used in the revised model



Appendix 4.10: Assumptions of proportional odds in the revised model

Stratifying the means of the predictors by the levels of the outcome:



Appendix 5.1: Recruitment methods to the VEMD and VAED

VEMD

The VEMD contains data from all 38 public hospitals with 24-hour EDs in Victoria. All first presentations are captured in the VEMD (patients who return to have pre-arranged visits are excluded). It is possible that patients could have more than one injury, and each injury is captured in the VEMD. Prior to 2012, the VEMD includes all patients treated in the ED for up to four hours (patients in the ED for over four hours are included in the VAED), but from 2012 all patients are included in the VEMD. Patients who are admitted to hospital from the ED or within 30 days are not included in the VEMD (they are captured in the VAED). ED data on patients includes their country of birth, area of residence, procedure/s performed, and a narrative summary of up to 250 characters (399).

VAED

The VAED contains data from all hospitals (public and private), rehabilitation centres, extended care facilities, and centres for day procedures in Victoria (400). All first daily admissions are captured in the VAED (patients with multiple admissions in one day and inter-hospital transfers are excluded). It is possible that patients could have more than one injury, and each injury is captured in the VAED. Hospital admission data on patients is coded to the external causes chapter of the ICD tenth revision, Australian modification (ICD-10-AM) (401).

Appendix 5.2: Methods of data extraction by VISU from the VEMD and VAED

ED presentations

The VISU identified patients presenting to EDs through a text search of the VEMD and the narrative summary. Searches were performed for 'description of event: cricket', and returned records were manually checked for relevance by the VISU. Records were then included if 'human intent: non-intentional harm' was listed. Any records which were 'return visit/s' or 'pre-arranged admission/s' were then excluded, to ensure only the incidence of injuries was captured, and records of patients <5 years were also excluded. Next, records which documented 'body region: hand and wrist' were included. Following this, ten year summary data was extracted for sex, age, anatomical location of injury on the hand or wrist, nature of injury as documented in the ED narrative summary, and cause of injury as documented in the ED narrative summary. Where summary data related to less than five patients, it was then excluded by the VISU, to ensure patient confidentiality. In the literature, an external validation study has previously been performed in the VEMD, comparing all injury data in the VEMD with patient reported data through in person interviews during the ED attendance. This study showed that 87% of records had ≥1 error, though validity was 90% for human intent and body region, both variables used to identify records for this study, and nature of injury, which was of particular importance in the results (351).

Hospital admissions

The team from the VISU identified patients admitted to hospital through a search of the VAED using ICD-10-AM codes. A search was performed for a 'principle diagnosis: community injury (S00-T75 or T78). Records were then excluded if 'external cause: intentional or undetermined event/s' was listed. Next, records which had 'activity code: cricket (U51.1)' were included, followed by patients aged ≥5 years, and 'body region: hand or wrist (S60-S69)'. Any records for patients which were transferred from another hospital were excluded, and re-admissions for day-treatments (for example, for blood transfusions) over the last 30 days were excluded, to prevent duplication of patients in the dataset. Following this, ten-year summary data was extracted for sex, age, nature of injury (coded from the ICD-10-AM), and cause of injury (coded from the ICD-10-AM). Where summary data related to less than five patients, it was then excluded by the VISU, to ensure patient confidentiality. To my knowledge, validation studies of the VAED have not yet been performed.

Appendix 5.3: Harmonisation of data from VEMD and VAED

Type of data	Data from VEMD	Data from VAED	Harmonisation of data for current study
Anatomical location of injury	Thumb	N/A	Thumb
	Index finger		Index
	First finger		
	Middle finger		Middle
	Second finger		
	Ring finger		Ring
	Third finger		
	Baby finger		Little
	Fourth finger		
	Finger not specified		Unspecified
	No mention of finger		
Type of injury	Fracture	Fracture	Fracture
	Dislocation/ Sprain/ Strain	Dislocation/ Sprain/ Strain	Dislocation
	Open wound	Open wound	Open wound
	Superficial injury	Superficial injury	Superficial injury
	Injury to muscle/ tendon	Injury to muscle/ tendon	Muscle injury
	Crushing injury	Crushing injury	Unspecified (including other) injury
	Injury to nerves	Injury to nerves	
	Injury to blood vessels	Injury to blood vessels	
	Burns	Intracranial injury	
	Other/ Unspecified injury	Injury to internal organs	
		Poisoning/ Toxic effects	
		Foreign body	
		Traumatic amputation	
		Other effects	
		Other/ Unspecified injury	
Cause of injury	Hit/ Struck/ Crush	Hit/ Struck/ Crush	Hitting injury
	Fall	Fall	Falling injury
	Cutting/ Piercing	Cutting/ Piercing	Unspecified (including other) injury
	Fires/ Burns/ Scalds	Over exertion	
	Transport	Transport	
	(Near) drowning	Foreign body	
	Natural environmental	Natural environmental	
	Poisoning	Other	
	Choking		
	Other		

Appendix 5.4: Number of participants with hand and wrist injuries presenting to hospital and participation-adjusted annual injury rates, in Victoria, Australia, from July 2007/8 to June 2017/18, inclusive

Cricket season	Number of hospital presentations			Number of cricketers	Participant-adjusted annual incidence rate per 10,000 cricketers		
	ED presentations n (%)	Hospital-admissions n (%)	Total hospital-treated cases n (%)		ED presentations (95% CI)	Hospital-admissions (95% CI)	Total hospital-treated cases (95% CI)
2007/8	397 (7.5)	351 (9.1)	748 (8.1)	188,615	21.0 (20.0-22.1)	18.6 (17.5-19.8)	39.7 (38.9-40.4)
2008/9	436 (8.2)	331(8.6)	767 (8.3)	197,454	22.1 (21.0-23.1)	16.8 (15.5-18.0)	38.8 (38.0 -39.6)
2009/10	447 (8.4)	303 (7.8)	750 (8.2)	208,349	21.5 (20.4-22.5)	14.5 (13.2 to 15.9)	36.0 (35.2-36.8)
2010/11	382 (7.2)	332 (8.6)	714 (7.8)	213,480	17.9 (16.7-19.1)	15.6 (14.3-16.8)	33.4 (32.6-34.3)
2011/12	441 (8.3)	358 (9.3)	799 (8.7)	214,393	20.6 (19.5-21.7)	16.7 (15.5-17.9)	37.3 (36.5-38.1)
2012/13	514 (9.6)	276 (7.1)	790 (8.6)	215,636	23.8 (22.8-24.9)	12.8 (11.4-14.2)	36.6 (35.8-37.5)
2013/14	527 (9.9)	361 (9.3)	888 (9.7)	261, 563	20.1 (19.1-21.2)	13.8 (12.4-15.2)	33.9 (33.1-34.8)
2014/15	578 (10.9)	369 (9.6)	947 (10.3)	257, 405	22.5 (21.4-23.5)	14.3 (13.0-15.6)	36.8 (36.0-37.6)
2015/16	554 (10.4)	394 (10.2)	948 (10.3)	263, 650	21.0 (19.9-22.1)	14.9 (13.6-16.3)	36.0 (35.1-36.8)
2016/17	566 (10.6)	379 (9.8)	945 (10.3)	309, 473	18.3 (17.1-19.4)	12.2 (10.8-13.7)	30.5 (29.6-31.4)
2017/18	485 (9.1)	407 (10.5)	892 (9.7)	359, 595	13.5 (12.1-14.8)	11.3 (9.8-12.8)	24.8 (23.8-25.8)
Overall	5,327 (100)	3,861 (100)	9,188 (100)	2,689,613	19.8 (18.7-20.9)	14.4 (13.0-15.7)	34.2 (33.3-35.0)

95% CI: 95% confidence interval; ED: Emergency department

Appendix 5.5: Recruitment methods to the CHWS

28,152 cricketers who were registered on the EWCB database and who had consented to be contacted for cricket-related research received an email inviting them to take part in the CHWS. 2,548 (9.1%) cricketers gave consent to participate in the CHWS. As players had not given consent for their data held on the EWCB database to be analysed for research purposes, it was not possible to ascertain the demographics of cricket players who did not consent to participate in the CHWS. Of those who consented to participate in the CHWS, 2,294 met eligibility criteria and were recruited to the CHWS (90.3%) (356).

Data for the CHWS was captured using an electronic questionnaire. The questionnaire was developed jointly by researchers, current and former cricketers, and the England and Wales Cricket Board. REDCap software (196, 402) hosted at the University of Oxford was used to administer the questionnaire, with assistance from an experienced database manager (356, 357, 403, 404). A pilot questionnaire was used on two current and two former cricketers, resulting in changes in wording, and was also used on three researchers to assess for errors (356, 357, 403, 404). Data captured on the CHWS questionnaire includes anthropometric data, self-reported medical history (including joint-specific osteoarthritis history), cricket-related playing history, and health-related quality of life questions (including those from the Short Form 8).

Appendix 5.6: Methods of data capture in the CHWS

<u>Ascertainment of Playing Status</u>

Playing status was assessed in the CHWS by asking participants 'Playing status?', with 'Currently playing cricket/ No longer playing cricket/ Plan to return to cricket' response options.

Ascertainment of Hand Injury

A history of significant hand injury was assessed in the CHWS by asking participants 'have you ever had any cricket-related injuries leading to more than four weeks of reduced participation in exercise, training or sport?', with 'Yes/ No' response options. If the 'Yes' response option was selected, branched logic was used to specify the site of injury, with 'Hip or groin/ Knee/ Ankle/ Shoulder/ Hand or finger/ Spine or back/ Other joint' response options. If the 'Hand or finger' response option was selected, branched logic was used to specify the side of the hand or finger injury, by asking participants 'How many left hand/ finger injuries have you had' with a numerical response option from 0 to 100. Similarly, they were asked 'How many right hand/ finger injuries have you had' with a numerical response option from 0 to 100.

Ascertainment of Hand Osteoarthritis

The primary outcome for the current study was a history of hand osteoarthritis. This was assessed in the CHWS by asking participants 'Have you ever been told by a doctor that you have osteoarthritis (wear and tear or joint degeneration)?', with 'Yes/No/ Don't know' response options. If the 'Yes' response option was selected, branched logic was used to specify the site of osteoarthritis, with 'Hip / Knee/ Ankle/ Shoulder/ Hand or finger/ Spine or back/ Other joint' response options. If the 'Hand or finger' response option was selected, branched logic was used to specify the side of the hand or finger osteoarthritis, by asking participants 'Which hand/ finger do you have osteoarthritis (wear and tear or joint degeneration) in?', with 'Left/ Right/ Both' response options.

Ascertainment of chronic hand pain

As the current study was a retrospective analysis, it was not possible to examine the participants for osteoarthritis. Therefore, as a way of validating the self-reported history of doctor diagnosed hand osteoarthritis, a history of chronic hand pain was used as the secondary outcome for the current study. Chronic hand pain was assessed in the CHWS by asking participants 'Do you currently experience pain, discomfort, or have any problems in your joints?', with 'Yes/ No/ Don't know' response options. If the 'Yes' response option was selected, branched logic was used to specify the site of the pain, discomfort or joint problems, by asking participants 'If yes, where?', with Hip or groin/ Knee/ Ankle/ Shoulder/ Hand or finger/ Spine or back/ Other joint' response options. If the 'Hand or finger' response option was selected, branched logic was used to specify the side of the hand or finger pain, by using the NHANES criteria (405). Participants were asked 'Have you had pain in your left hand or finger on most days of the last month?', with 'Yes/No' response options. Similarly, participants were asked 'Have you had pain in your right hand or finger on most days of the last month?', with 'Yes/No' response options.

Age: Age was captured in the CHWS by asking participants their date of birth and age at time of questionnaire completion.

Exposure to playing cricket: Exposure to playing cricket was also captured in the CHWS, by asking participants both about a) their length of cricket participation, and b) their standard of playing cricket. The length of cricket participation was captured by asking 'Approximately how many seasons have you played cricket for?' (numerical response). The standard of playing cricket was captured by asking 'What was the highest standard of cricket that you played for at least one season?', with 'International/ County or Premier league/ Academy/ County-age-group/ University/ School/ Village or Social/ Don't know' response options.

Handedness: Handedness when playing cricket was captured in the CHWS by asking participants 'When you bowl or throw do you use your right or left hand?', with 'Left/ Right/ Both/ Don't know' response options.

Appendix 5.7: Frequency tables for the number of cricket players with hand injury and hand osteoarthritis or pain

Ipsilateral Hand osteoarthritis:
All cricketers, N= 3,786
All hands (hand-level analysis – i.e.- 2 hands per participant)

		Outcome variable Ipsilateral Hand osteoarthritis	
		Yes	No
Hand injury	Yes N= 630	38 (6.0%)	592 (94.0%)
	No N= 3156	92 (2.9%)	3064 (97.1%)

Hand osteoarthritis Subgroup analysis:
All cricketers, N= 1,866 (15 current and 12 former cricketers excluded)

Dominant hand:

		Outcome variable Hand osteoarthritis	
		Yes	No
Hand injury	Yes N= 247	18 (7.3%)	229 (92.7%)
	No N= 1619	55 (3.4%)	1564 (96.6%)

Non-dominant hand:

		Outcome variable Hand osteoarthritis	
		Yes	No
Hand injury	Yes N= 228	14 (6.1%)	214 (93.9%)
	No N= 1638	40 (2.4%)	1598 (97.6%)

Hand pain:
Former cricketers, N= 1,688
All hands (hand-level analysis – i.e.- 2 hands per participant)

		Outcome variable Ipsilateral Hand pain	
		Yes	No
Hand injury	Yes N= 244	34 (13.9%)	210 (86.1%)
	No N= 1444	104 (7.2%)	1340 (92.8%)

Hand Pain Subgroup analysis:
Former cricketers, N= 832 (12 former cricketers excluded)

Dominant hand:

		Outcome variable Hand pain	
		Yes	No
Hand injury	Yes N= 90	14 (15.6%)	76 (84.4%)
	No N= 742	61 (8.2%)	681 (91.8%)

Non-dominant hand:

		Outcome variable Hand pain	
		Yes	No
Hand injury	Yes N= 83	11 (13.3%)	72 (86.7%)
	No N= 749	49 (6.5%)	700 (93.5%)